Simulated Cervical Acoustic Radiation Force Impulse (ARFI) Imaging

by

Andrew Homyk

Department of Biomedical Engineering
Duke University

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Mark L. Palmeri, Supervisor

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Kathryn R. Nightingale

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Lori A. Setton

Thesis submitted in partial fulfillment of
the requirements for the degree of Master of Science in the Department of
Biomedical Engineering in the Graduate School
of Duke University

2011
ABSTRACT

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Abstract

Every day, 1,300 children in the U.S. and an additional 34,000 children worldwide are born prematurely. This study acts as a feasibility study for a proposed ultrasonic technique for the identification of preterm birth risk factors using an acoustic technique known as Acoustic Radiation Force Impulse (ARFI) imaging. A 3D finite element model was constructed to optimize transducer ARFI parameters in a layered cervix structure prior to clinical evaluation. The transducer model optimized in this study was the AcuNav™ (Siemens Medical Solutions, Mountain View, CA). Cervix model structural geometry and material properties were varied according to anticipated pregnancy induced property fluctuation. Transmitted ARFI acoustic fields were generated by applying a Field II derived pulse to the 3D model[15]. Optimization procedures were performed in the following order: focal depth evaluation, transmit frequency optimization, effect of material property variation and the application of ARFI shear wave speed calculation algorithms to a layered cervical structure. Results indicated that ARFI evaluation of a layered cervix structure was most feasible using an 8MHz transmit frequency in the focal range of 5-10mm axial depth. It was observed that material property estimation errors were most likely when ARFI excitations were focused near a material boundary. A phenomenon was noted where shear waves initiated in stiffer media were slowed as a function of their relative proximity to a more
compliant medium. Overall, these simulation studies demonstrate that ARFI shear wave imaging in the cervix is feasible; a model has been developed that can be used to evaluate the accuracy of shear stiffness estimates in the cervix to help address the important clinical problem of premature cervical ripening.
Contents

Abstract ......................................................................................................................................................... iv

List of Tables .................................................................................................................................................. viii

List of Figures ................................................................................................................................................ ix

1. Introduction .............................................................................................................................................. 1
   1.1 History of Preterm Birth Evaluation ............................................................................................... 1
   1.2 Present Study ..................................................................................................................................... 3

2. Methodology ........................................................................................................................................... 7
   2.1 Model Creation .................................................................................................................................. 7
      2.1.1 Model Assumptions .................................................................................................................. 10
      2.1.2 Material Property Selection .................................................................................................... 12
      2.1.3 Anatomical Relevance ............................................................................................................ 13
   2.2 Convergence ....................................................................................................................................... 13
   2.3 Focal Depth Evaluation .................................................................................................................... 16
      2.3.1 Maximum Displacements on the Lateral-Axial Plane ............................................................ 17
      2.3.2 Maximum Displacements along Axial Depth ......................................................................... 17
   2.4 Frequency Analysis ............................................................................................................................ 18
   2.5 Material Property Variation ............................................................................................................. 19
   2.6 Shear Wave Speed Tracking ............................................................................................................ 19

3. Results ...................................................................................................................................................... 22
   3.1 Maximum Displacements on the Lateral-Axial Plane ....................................................................... 22
3.2 Maximum Displacements along Axial Depth ................................................. 24
3.3 Frequency Analysis ....................................................................................... 26
3.4 Material Property Variation .......................................................................... 27
3.5 Shear Wave Speed Tracking ......................................................................... 29
4. Discussion ........................................................................................................ 37
References .......................................................................................................... 43
List of Tables

Table 1 – The table below is a listing of transducer parameters used for the convergence analysis of the cervix 3D model; these parameters are typical of those used in experimental investigations using the AcuNav™ transducer.................................14

Table 2 – Mesh Density Comparison based on maximum ARFI push evaluation. Since the 0.015cm mesh was determined to be too computationally intensive to be practical, it was used as a baseline for mesh evaluation. A mesh size of 0.025cm was selected for all subsequent studies as it fell within 7.0% of the 0.015cm case and took up a considerably smaller amount of RAM than the 0.02cm case..........................................................15

Table 3 – Cervix material properties defined by layer. Poisson’s Ratio was set to 0.499 for each layer. Short description of layer composition included based on literature[22]...........18

Table 4 – Cervix material property case evaluations. Case 1 simulates a stiff central layer that would be expected early in pregnancy when the cervical collagen has not begun to denature due to prostaglandin. Case 2 represents a more compliant outer layer in the situation that the connective tissue is more dispersive than the rest of the cervical tissue. Case 3 represents an inner layer next to the cervical canal that is more compliant than the encompassing tissue.................................................................19

Table 5 – Percent error in the RANSAC calculation of the Young’s modulus of the central layer. Note how the error increases significantly once the central layer exceeds an $E_y = 5\text{kPa}$..........................................................32

Table 6 - Percent error in the RANSAC calculation of the Young’s modulus of the inner layer, which was modeled as 5kPa. Note how the error decreases once the central layer exceeds an $E_y = 5\text{kPa}$ ..........................................................33
List of Figures

Figure 1 – Graphic rendering of anticipated ARFI imaging clinical application. A Siemens AcuNav™ catheter-based transducer will transmit acoustic pulses into the uterine cervix to evaluate material properties. The iso-Contours of color in the cervical tissue represent shear wave displacement fields propagating away from the region of acoustic radiation force excitation. .................................................................................................................. 4

Figure 2 – Modified histology image of a cervical cross-section; the specimen is colored to highlight the three fundamental zones within the cervix: Orange – Outer Layer, Magenta – Central Layer, Green – Inner Layer. This image was adapted, with permission, from the work of Dr. Valentin Martin, Autonomous University of Barcelona[18]........................................................................................................................................... 5

Figure 3 – 3D cervix model consists of three seamless, independently defined layers within the mesh structure: the Outer Surface, the Central Layer and the Layer Adjacent to the Cervical Canal. Axes are defined: z – axial, x – lateral, y – elevation. Layer thicknesses and canal dimensions are representative of those found in hysterectomy specimens (2.1.3 Anatomical Relevance). ........................................................................................................ 7

Figure 4 – Acoustic force impulse applied with a 45µsec step function at the beginning of each simulation to create a propagating wave. ........................................................................................................ 8

Figure 5 – Example node surrounded by four 8-node elements. Volume attributed to this node will be the average volume of all four surrounding elements. ..................................................... 9

Figure 6 – Three hyper-Pyramids constructed out of a single 8-node element. The volume of each pyramid can be found by using plane equations[12]. ................................................................. 9

Figure 7 - Resulting nodal z-displacements through time following a simulated ARFI push. Dimensions in the legend represent mesh size. Displacements at the focal point, (0,0,10mm) and a point 5mm lateral to the focal point (5,0,10mm). Convergence was achieved at 0.025mm mesh size (green line). ......................................................................................... 16

Figure 8 – Maximum axial displacements that occurred on the lateral-axial surface of the simulation model. Note that greater negative displacements correspond to higher nodal displacements due to model orientation, in this case. This particular example simulated an ARFI pulse focused at an axial depth of 1.2 cm, indicated by arrow. ........................................... 22
Figure 9 – An average of all the maximum displacement values was taken for each of the sixteen simulations and plotted above. Peak amplitudes corresponding to each push were also recorded.

Figure 10 - Focal depth evaluation performed using a 6MHz impulse transmission frequency. Each curve represents an individual ARFI simulation. Sixteen simulations were performed at focal depths increasing from 2 to 17mm. A single curve indicates the maximum displacement experienced by each node along the axial line of ARFI excitation.

Figure 11 - Focal depth evaluation performed using 12MHz (top) and 8MHz (bottom) impulse frequencies. Each curve represents an individual ARFI simulation. Sixteen simulations were performed at focal depths increasing from 2 to 17mm. A single curve indicates the maximum displacement experienced by each node along the axial line of ARFI excitation.

Figure 12 – Normalized axial displacement profiles in simulated layered cervix with Young’s moduli ranging from 1-10 kPa. The ARFI excitations were either focused at 4 or 12mm. The Young’s moduli of the three cervix layers were modified to determine the effects that heterogeneity has on the displacement response. Layer stiffnesses of the model are listed on the legend in this order: Adjacent to Canal, Central Layer, Outer Surface.

Figure 13 – Young’s moduli calculated by RANSAC algorithm for the inner layer of tissue (E = 5kPa) using two methods: TTP and TTPS. The ARFI excitation was focused at the midpoint of the inner layer (4.5mm axial depth, see left image). The Young’s Modulus of the central layer was varied from 1-10kPa and the outer layer was kept constant (E=5kPa). Since shear wave estimation was performed in the inner layer, the actual Young’s modulus for each simulation should be close to 5kPa.

Figure 14 - Young’s moduli calculated by RANSAC algorithm for the material boundary between the inner (E = 5kPa) and central layer of tissue (E = 1-10kPa) using two methods: TTP and TTPS. ARFI excitation was focused between layers (7.0mm axial depth, see left image). Young’s modulus of the outer layer was kept constant (E = 5kPa).

Figure 15 - Young’s moduli calculated by RANSAC algorithm for the central layer of tissue (E = 1-10kPa) using two methods: TTP and TTPS. ARFI excitation was focused at the midpoint of the central layer (9.5mm axial depth, see left image). Young’s Modulus of the inner and outer layers were kept constant (E = 5kPa).
Figure 16 – Percentage of inliers that composed the RANSAC fitted plane. This plane was used to calculate shear wave speed for an ARFI excitation focused at 4.5mm. 34

Figure 17 - Percentage of inliers that composed the RANSAC fitted plane. This plane was used to calculate shear wave speed for an ARFI excitation focused at 7.0mm. 34

Figure 18 - Percentage of inliers that composed the RANSAC fitted plane. This plane was used to calculate shear wave speed for an ARFI excitation focused at 9.5mm. 35

Figure 19 – Shear wave propagating through layered cervix model develops an angled trajectory associated with the material variation between isotropic layers. In this case the central layer had a Young’s modulus of 1kPa and the inner layer had a Young’s modulus of 5kPa. 40
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1. Introduction

Every day, 1,300 children in the U.S. and an additional 34,000 children worldwide are born prematurely (< 37 weeks). Although many of these children grow up to live fulfilling lives, a large percentage of them suffer from debilitating conditions such as cerebral palsy, physical deformities or, in some cases, infant mortality. Cervical insufficiency has been shown to be intimately linked with the prevalence of preterm birthing events. Accurate and early identification of a cervical insufficiency during pregnancy may prove paramount in the development of effective preventative measures and clinical techniques.

1.1 History of Preterm Birth Evaluation

Early researchers in this field recognized that the softening of the uterine cervix is an indicator of when birth will occur. The “Hegar Sign” was first described in 1895 by Hegar and Reinl as an indicator of cervical softening. This softening has been shown to be linked with micro-structural changes in the collagen orientation of the cervix. As the collagen shifts within the extracellular framework of the cervix, the circumferential stiffness of the cervix weakens, eventually allowing cervical dilation and childbirth.

In the 1960’s, a clinical researcher, one Dr. E. H. Bishop, apparently grew weary of the unpredictability associated with the preterm birthing events of his patients. Thus, he sought to develop a quantifiable method for evaluating the competency of the uterine cervix. Over the next several years, Bishop developed a digital scoring technique that
related several observed gross anatomical changes with some quantifiable cervical parameters, such as: cervix consistency, dilation, effacement, cervix orientation and fetal position. High scores (8-9) indicated that a birthing event could spontaneously occur, while lower scores indicated that the women would likely require an applied cervical ripening method to induce labor. Although developed almost fifty years ago, the Bishop score is still widely used, despite many aspects of the scoring technique being based solely on subjective assessment.

In the advent of the 21st century, ultrasonographic and elastography methods began to play a key role in preterm birth evaluation. In the late 1980’s and early 1990’s, sonographers began evaluating the length of the cervix throughout pregnancy. Transvaginal ultrasonic transducers were used to create images of the uterine cervix at various phases of pregnancy; the apparent cervix length and level of funneling were recorded in several investigations[3][13][14][25]. The results of these studies indicate that changes in cervical length can be used to effectively predict preterm birth in, reportedly, up to 76% of cases. Although the success rate of this technique varies by study, it represents the first step in developing a quantitative determination of preterm labor risk.

Despite the relative success of the aforementioned cervical assessment techniques, there is still no widely accepted quantitative, clinical method for evaluating cervical softness. Cervical palpation techniques can be effective in determining softening of the cervix, but are inherently subjective. Digital imaging techniques using
sonography, although providing some quantitative measure of cervical length, do not account for anatomical variability nor do they provide insight into the structural integrity of the cervix itself.

1.2 Present Study

This study is a feasibility analysis for a proposed technique that intends to quantify the stiffness of the uterine cervix throughout pregnancy. Acoustic radiation force impulse (ARFI) imaging is a well-established ultrasonic method for remotely applying an acoustic “push” to a targeted area of tissue\textsuperscript{[7][11][23]}. Displacements caused by this acoustic “push” can be monitored and tissue mechanical properties can be extracted based on observed shear waves in the tissue. The speed of these shear waves can be tracked and used to find the shear modulus of the tissue under interrogation according to the following equation:

\[ c_T = \sqrt{\frac{\mu}{\rho}} : \mu = \frac{E}{2(1+\nu)} \]

Where: \( c_T \) – shear wave speed [m/s], \( \mu \) - shear modulus [Pa], \( \rho \) – density of medium [kg/m\textsuperscript{3}], \( E \) – Young’s modulus [Pa], \( \nu \) – Poisson’s ratio

The proposed clinical study will use a catheter based AcuNav\textsuperscript{TM} (Siemens Medical Solutions, Mountain View, CA) transducer to apply an acoustic push to the various anatomical layers of the cervix, see Figure 1. For further information on specific
AcuNav™ transducer parameters, the reader is referred to Proulx et al[29]. We hypothesize that by evaluating the mechanical properties of the cervical layers during pregnancy, new light can be shed on the mechanisms and likelihood of preterm birthing events.

Figure 1 – Graphic rendering of anticipated ARFI imaging clinical application. A Siemens AcuNav™ catheter-based transducer will transmit acoustic pulses into the uterine cervix to evaluate material properties. The iso-contours of color in the cervical tissue represent shear wave displacement fields propagating away from the region of acoustic radiation force excitation.

The human uterine cervix is composed of three fundamentally different, seamless layers: the connective outer surface, a collagenous central layer and a thin endothelial layer adjacent to the os – the central canal of the cervix, see Figure 2. The
structural integrity of each layer is likely of great importance in maintaining the competence of the cervix during pregnancy. The complications associated with having a multilayered structure also play a key role in the development of this feasibility study.

Figure 2 – Modified histology image of a cervical cross-section; the specimen is colored to highlight the three fundamental zones within the cervix: Orange – Outer Layer, Magenta – Central Layer, Green – Inner Layer. This image was adapted, with permission, from the work of Dr. Valentin Martin, Autonomous University of Barcelona[18]

A 3D finite element model of the cervix was made in order to mathematically determine the response of a multilayered, possibly anisotropic material to an ARFI excitation. One might ask: Why is a finite element model necessary to validate a cervical assessment method that could be performed empirically? The clinical acquisition and preparation of structurally relevant hysterectomy specimens for ex vivo experimentation is not only cost and time prohibitive, but can also entail a great deal of experimental
variability. Also, specific ultrasonic ARFI excitation parameters need to be optimized before performing any sort of large scale clinical trial.

Using a finite element technique allows for the optimization of several acoustic parameters based on anticipated anatomical variation that we could encounter. Thusly, this study sought to answer four key research questions, which were thought critical to the development of a novel method for identifying cervical insufficiency.

1) What ultrasonic focal configuration should be used to achieve the greatest ARFI imaging contrast?

2) After identifying an optimum focal range, what ultrasonic transmit frequency will likely provide the best ARFI imaging result?

3) What effect does material property variation within the layers of the cervix have on ARFI impulses?

4) Using ARFI imaging algorithms currently used in vivo, is it possible to extract independent layer material property values?

The answers to these key research questions were hypothesized to provide necessary insight into the feasibility of the proposed ultrasonic technique. Should the proposed technique be proven valid, it is anticipated that the mechanical property measurements obtained from ARFI excitations will serve as a quantitative evaluation for cervical insufficiency.
2. Methodology

2.1 Model Creation

LS-DYNA3D 3.1\(^{[17]}\) and Altair HyperMesh 10.0\(^{[2]}\) were used to generate a 3D, quad-symmetric, layered, cervix model based upon laboratory measurements of hysterectomy specimens, see Figure 3. Boundary conditions were applied to the model based on assumptions and known constraints (Section 2.1.1). Material properties were selected based on a range of values obtained from relevant scientific literature. Young’s modulus ranged from 1kPa to 10kPa and Poisson’s ratio was 0.499 as the material was assumed incompressible\(^{[21][22][26][28]}\). Element size was determined by a convergence analysis (2.2 Convergence).

![3D cervix model](image)

Figure 3 – 3D cervix model consists of three seamless, independently defined layers within the mesh structure: the Outer Surface, the Central Layer and the Layer Adjacent to the Cervical Canal. Axes are defined: z – axial, x – lateral, y – elevation.
Layer thicknesses and canal dimensions are representative of those found in hysterectomy specimens (2.1.3 Anatomical Relevance).

ARFI excitations in the model were generated using Field II\textsuperscript{15} to calculate the intensity profile of acoustic forces, given specified transducer input parameters. These acoustic forces were applied to each node within the intensity profile as point forces acting in the axial direction. A ramped step function was used to explicitly apply the acoustic point forces, see Figure 4.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{impulse_amplitude_function.png}
\caption{Acoustic force impulse applied with a 45\textmu sec step function at the beginning of each simulation to create a propagating wave.}
\end{figure}

Forces calculated by Field II for each node, act as body forces based on the following equation:

\[ F = \frac{2\alpha I}{c} \frac{\text{dyn}}{\text{cm}^3} \]

Where: \( \alpha \) – Attenuation \( \frac{\text{Np}}{\text{cm}} \); \( I \) – Time Average Intensity \( \frac{\text{W}}{\text{cm}^2} \)
In order to convert these body forces [dyn/cm$^3$] into point forces [dyn] it was necessary to establish an average volume of all the arbitrarily sized, 8-node, elements surrounding each particular node, see Figure 5.

Figure 5 – Example node surrounded by four 8-node elements. Volume attributed to this node will be the average volume of all four surrounding elements.

Determining the exact volume of each arbitrarily shaped, 8-node element was not trivial and was accomplished by dividing each element into three unique hyper-pyramids, see Figure 6.

Figure 6 – Three hyper-pyramids constructed out of a single 8-node element. The volume of each pyramid can be found by using plane equations\cite{12}.  

\[ c = \text{Speed of Sound} \left[ \frac{\text{cm}}{s} \right] \]
To find the volume of each hyper-pyramid:

\[
Volume = \frac{1}{3} A_{\text{base}} h
\]

1) The area of each base was found using the equation for a generic 4 sided polygon:

\[
A_{\text{base}} = \sqrt{(s - a)(s - b)(s - c)(s - d) - \frac{1}{4}(ac + bd + pq)(ac + bd - pq)}
\]

Where: a, b, c, d are the length of the sides; p, q are the diagonals ; \( s = \frac{a + b + c + d}{2} \)

2) The height of the pyramid was found by establishing a planar equation for the base, and calculating the distance from the base plane to the apex of the pyramid.

\[\text{Equation of the base plane was in the form: } Ax + By + Cz + D = 0\]

\[h = \text{abs} \left( \frac{Ax_{\text{apex}} + By_{\text{apex}} + Cz_{\text{apex}} + D}{\sqrt{A^2 + B^2 + C^2}} \right)\]

The volume of the three internal hyper-pyramids was found for each element in the cervix model and summed to determine the exact volume of each element. A specific volume number was then attributed to each node based on the average of all the elements that that node was a part of.

\[\text{2.1.1 Model Assumptions}\]

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \delta x,y,z )</td>
<td>Nodal Displacement</td>
</tr>
<tr>
<td>Rx,y,z</td>
<td>Nodal Rotation</td>
</tr>
<tr>
<td>xo</td>
<td>Initial Lateral Position</td>
</tr>
<tr>
<td>yo</td>
<td>Initial Elevation Position</td>
</tr>
<tr>
<td>zo</td>
<td>Initial Axial Position</td>
</tr>
<tr>
<td>t</td>
<td>Time</td>
</tr>
<tr>
<td>DOF</td>
<td>Depth of Field</td>
</tr>
</tbody>
</table>
Cervix geometry can be represented by a quarter-cylinder with symmetry planes on the XZ, YZ and XY planes.

\[
\begin{align*}
    \begin{cases}
        x_0 = 0 : & \begin{cases} \delta x = 0 \\ R_x = 0 \\ R_z = 0 \\ \delta y = 0 \end{cases} \\
        y_0 = 0 : & \begin{cases} R_x = 0 \\ \delta y = 0 \\ R_z = 0 \end{cases} \\
        z_0 = 0 : & \begin{cases} \delta z = 0 \\ R_x = 0 \\ R_y = 0 \end{cases}
    \end{cases}
\]

Traveling shear waves will not reflect off of the uterus within ARFI time frame

\[ z_0 = L : \text{Non-Reflecting Boundary}^{1} \]

The cervix is fixed at the uterus attachment

\[ z_0 = L : \begin{cases} \delta x = 0 \\ \delta y = 0 \\ \delta z = 0 \end{cases} \]

The time frame of ARFI is too short for tissue to exhibit significant viscoelasticity\(^2\)

\[ \text{Linearly Elastic Isotropic Solid} \]

\(^1\) Non-reflecting boundary conditions simulate a semi-infinite medium by applying Laplace derived equations to negate the effects of a propagating wave\(^1\).

\(^2\) Viscosity may have a role in shear wave propagation, but its higher-order effects will be neglected in this study.
 ➢ Cervix layers are seamlessly connected with no-slip interfaces

\[
\text{Elements between layers are tied together}
\]

 ➢ AcuNav\textsuperscript{TM} transducer placement causes no initial displacement or pre-strain

\[
t = 0 : \begin{cases}
\delta x = 0 \\
\delta y = 0 \\
\delta z = 0
\end{cases}
\]

 ➢ Acoustic radiation forces act solely in the axial direction

\[
F_{x,y} = 0
\]

 ➢ AcuNav\textsuperscript{TM} is unfocused in the elevation direction

### 2.1.2 Material Property Selection

Material properties were selectively identified from previous scientific work by closest experimental relevance. Although not an extensively researched field, a range of Young’s moduli for the pregnant cervix and nearby uterine tissue has been found to be in the range of 1kPa-7kPa at 10% unconfined compressive strain\textsuperscript{[21][22]}. Another study, measuring the mechanical properties of non-pregnant cervix specimens to failure, found Young’s moduli in the range of 2MPa-10MPa at tensile strains of 20-40%\textsuperscript{[28]}.  

In terms of relevance, ARFI imaging typically induces very small displacements in living tissue – in the range of 5-10\textmu m, depending on the application\textsuperscript{[26]}. In the case of this experiment, if an acoustic radiation force excitation were to induce 40\textmu m of axial displacement, that would amount to 0.25\% strain. Since the simulation will involve such low strains, it was assumed that the cervix will react in a manner similar to the 10\%
strain unconfined compressive experiment[21][22]. As a consequence, material Young’s modulus was evaluated in the range of 1kPa-10kPa.

It has been previously shown that muscle and other body tissues typically exhibit near-incompressibility; therefore the Poisson’s ratio was chosen to be 0.499 for all simulations[27].

2.1.3 Anatomical Relevance

In order to represent the three anatomical layers within the 3D cervix model, elements were separated into groups based on their radial distance from the central canal. Material properties could be independently assigned to each of these groups.

In terms of geometry, os radius and cervix outer radius were modeled to be 2mm and 17mm, respectively. This was based on measurements from hysterectomy specimens performed by our colleagues at the University of Wisconsin-Madison[9]. Cervix length (x – direction, Figure 3) is an interesting consideration as this dimension changes over the course of pregnancy. In a process called cervical funneling, the length of the closed cervix has been shown to reduce to <25mm in cases where pre-term birth is more likely[8]. As this seems to be a worst-case scenario for internal wave reflections, the length of the cervix model was set to 12mm, representing a 24mm long cervix.

2.2 Convergence

A convergence analysis was performed to determine the largest element spacing that could be used to generate an accurate ARFI simulation. Elements in the model were
defined as rectilinear 8-node elements that are near cubic in shape. Defining the elements as rectilinear as opposed to tetrahedral reduces a locking phenomenon associated with tetrahedral elements in shear. This allows for the use of larger elements, reducing the computational overhead concomitant with finer mesh structures\(^6\).

To achieve convergence, the cervix was modeled as a homogeneous, linearly elastic isotropic solid with three independent layers. Independent layer moduli were all set to 5kPa for this mesh study. The transducer excitation was simulated based on a 64 element AcuNav™ catheter transducer made by Siemens Corporation. Transducer parameters used are shown in Table 1.

Table 1 – The table below is a listing of transducer parameters used for the convergence analysis of the cervix 3D model; these parameters are typical of those used in experimental investigations using the AcuNav™ transducer.

<table>
<thead>
<tr>
<th>Ultrasound Transducer Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focus</strong></td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
</tr>
<tr>
<td><strong>Attenuation</strong></td>
</tr>
</tbody>
</table>

Using a fixed model geometry shown in Figure 3, mesh density was varied by methodically decreasing the average element size from 0.050cm to 0.015cm. An ARFI simulation was performed for each mesh density and the resulting nodal z-displacements were mapped through time for two nodes in the mesh structure: the node at the focus of the ARFI push and a second node 5mm lateral to the focus, see Figure 7.
Convergence was determined to be achieved when maximum push displacement fell within 7.0% of the 0.015cm mesh which was determined to exhibit exceptional computational overhead, see Table 2.

Table 2 – Mesh Density Comparison based on maximum ARFI push evaluation. Since the 0.015cm mesh was determined to be too computationally intensive to be practical, it was used as a baseline for mesh evaluation. A mesh size of 0.025cm was selected for all subsequent studies as it fell within 7.0% of the 0.015cm case and took up a considerably smaller amount of RAM than the 0.02cm case.

<table>
<thead>
<tr>
<th>Mesh Density (cm)</th>
<th>% Difference Fine Mesh</th>
<th>Runtime (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.015</td>
<td></td>
<td>92.2</td>
</tr>
<tr>
<td>0.02</td>
<td>-0.88%</td>
<td>21.5</td>
</tr>
<tr>
<td>0.025</td>
<td>6.14%</td>
<td>13.9</td>
</tr>
<tr>
<td>0.0375</td>
<td>8.77%</td>
<td>3.3</td>
</tr>
<tr>
<td>0.04</td>
<td>16.67%</td>
<td>2.1</td>
</tr>
<tr>
<td>0.045</td>
<td>28.07%</td>
<td>1.1</td>
</tr>
<tr>
<td>0.05</td>
<td>35.08%</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Figure 7 - Resulting nodal z-displacements through time following a simulated ARFI push. Dimensions in the legend represent mesh size. Displacements at the focal point, (0,0,10mm) and a point 5mm lateral to the focal point (5,0,10mm). Convergence was achieved at 0.025mm mesh size (green line).

2.3 Focal Depth Evaluation

In order to identify the optimum focal depth to use for ARFI imaging of the cervix, two types of analyses were performed. The first evaluated the maximum displacements experienced on the X-Z (lateral-axial) plane using sequential focal configurations (2.3.1 Maximum Displacements on the Lateral-Axial Plane). The second
analysis was similar, but considered maximum displacements experienced along the axial line of the push (2.3.2 Maximum Displacements along Axial Depth).

### 2.3.1 Maximum Displacements on the Lateral-Axial Plane

In order to determine the ideal focal configuration for ex vivo cervical ARFI experimentation, 16 simulations were performed. For each simulation, an ARFI displacement field was applied to the cervix model at a given focal depth using all sixty-four elements of the simulated array. Focal depths were varied from 2mm to 17mm – from the base of the cervical os to the outer surface, respectively. The maximum z-displacement, through time, was found for each node on the XZ plane.

The cervix was modeled as a fully homogeneous linear elastic, isotropic, incompressible solid. Young’s modulus was set to 4.5kPa for all three layers of the cervical structure. The ARFI excitation duration in this simulation was set to 45μsec with a 0.010 second simulation termination time.

### 2.3.2 Maximum Displacements along Axial Depth

In a second effort to develop a method for evaluating different focal configurations, sixteen simulations were performed in a manner identical to the previously described methodology in Section 2.3.1 Maximum Displacements on the Lateral-Axial Plane, with one exception. Instead of plotting the resulting maximum displacements over a plane, the maximum z-displacements were plotted for each node.
on the axial line of cervix model – along the z-axis, in line with the push. This allows for
the visualization of push’s displacement distribution and concentration.

2.4 Frequency Analysis

The next phase of simulation sought to identify which ultrasonic transmit
frequency would provide the best empirical ARFI data in the cervix. Similar to Section
2.3.2 Maximum Displacements along Axial Depth, sixteen simulations were performed
at each of two additional transmit frequencies: 8MHz and 12MHz. Cervical material
properties were refined based on new clinical observations from our collaborators, see
Table 3. Attenuation for the cervix model was set to 1.3 dB/cm/MHz\(^9\). For this set of
tests an experimental AcuNav\(^\text{TM}\) transducer was simulated, comprised of 192 linear
array elements with an arbitrarily set \(I_{sppa}\) of 1000W/cm\(^2\). Since these models are linear,
the results presented herein can be scaled to more realistic acoustic output intensities
when those values are available.

Table 3 – Cervix material properties defined by layer. Poisson’s Ratio was set to 0.499
for each layer. Short description of layer composition included based on literature\(^{22}\).

<table>
<thead>
<tr>
<th>Layer</th>
<th>(E_Y)</th>
<th>Layer Thickness</th>
<th>Layer Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner</td>
<td>5kPa</td>
<td>2mm</td>
<td>Endotheleal Cell Lining</td>
</tr>
<tr>
<td>Central</td>
<td>10kPa</td>
<td>12mm</td>
<td>Close-knit Collagen</td>
</tr>
<tr>
<td>Outer</td>
<td>1kPa</td>
<td>1mm</td>
<td>Loose Connective Tissue</td>
</tr>
</tbody>
</table>

For each set of focal depth simulations, maximum z-displacements were found
for each node on the axial line of cervix model.
2.5 Material Property Variation

The third phase of this study aimed to discover the effects that changing the material properties of the cervix layers would have on an applied ARFI pulse. Three material property cases were investigated based on anticipated anatomical variation, see Table 4.

Table 4 – Cervix material property case evaluations. Case 1 simulates a stiff central layer that would be expected early in pregnancy when the cervical collagen has not begun to denature due to prostaglandin. Case 2 represents a more compliant outer layer in the situation that the connective tissue is more dispersive than the rest of the cervical tissue. Case 3 represents an inner layer next to the cervical canal that is more compliant than the encompassing tissue.

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner</td>
<td>5kPa</td>
<td>5kPa</td>
<td>1kPa</td>
</tr>
<tr>
<td>Central</td>
<td>10kPa</td>
<td>5kPa</td>
<td>5kPa</td>
</tr>
<tr>
<td>Outer</td>
<td>5kPa</td>
<td>1kPa</td>
<td>5kPa</td>
</tr>
</tbody>
</table>

Cervix model layer thickness dimensions were maintained from the frequency analysis, see Table 3. Once again, an experimental AcuNav™ transducer was simulated with 192 linear array elements, and tissue attenuation set to 1.3 dB/cm/MHz. A transmission frequency of 8MHz was used to interrogate two focal regions at axial depths of 4 and 12mm. These focal regions were selected because they represent the extremes of the 8MHz focal range. At each focal depth, an ARFI pulse was simulated using all 192 elements and an arbitrarily set $I_{sppa}$ of 1000W/cm².

2.6 Shear Wave Speed Tracking
In this final phase of simulation, displacement data from simulated cervical ARFI was reformatted and evaluated using an in-house MATLAB (The MathWorks, Natick, MA, USA) tool utilizing Random Sample Consensus (RANSAC) methods. The RANSAC algorithm generates a shear modulus estimate in a region of interest using propagating shear wave data from an impulsive acoustic radiation force excitation. For further information and a complete explanation of the RANSAC shear wave speed estimation technique, the reader is directed to Wang et al[32].

For this investigation, the cervix model was divided into three concentric layers, each 5mm thick. The stiffness of the central layer was varied from 1kPa to 10kPa. The inner and outer layers were maintained at a stiffness of 5kPa. ARFI data sets were generated by performing simulations using three focal configurations focused at 4.5mm, 7.0mm and 9.5mm – the midpoint of the inner layer, the border of the inner and central layer, and the midpoint of the central layer, respectively.
Each set of ARFI data included the z-displacement values for nodes, through time, within a defined region of interest (ROI). The ROI is defined by the transducer’s depth of field (DOF) and the lateral extent of the simulation model (12mm in this case). The DOF for this analysis was defined by the following equation:

\[
\text{DOF} = \frac{8F}{\#^2 \lambda} = 1.52\text{mm}
\]

Where: \( F/\# = 1.0 \pm 0.05 \) and \( \lambda = \frac{c}{f} = 0.193\text{mm} \) for all simulations.

The simulation generated ARFI data sets were reformatted and run through a RANSAC analysis using two evaluation methods: time to peak (TTP) and time to peak slope (TTPS)\textsuperscript{[30]}. Shear modulus estimations and inlier percentages were recorded based on the RANSAC output for each simulation.
3. Results

3.1 Maximum Displacements on the Lateral-Axial Plane

Maximum axial displacements were recorded for each node on the lateral-axial plane of each simulation, see Figure 8.

Figure 8 – Maximum axial displacements that occurred on the lateral-axial surface of the simulation model. Note that greater negative displacements correspond to higher nodal displacements due to model orientation, in this case. This particular example simulated an ARFI pulse focused at an axial depth of 1.2 cm, indicated by arrow.

An average was taken of the maximum z-displacements recorded over the extent of the lateral-axial plane. This was performed for all sixteen simulations, in an attempt to
quantify distribution and amplitude of the shear wave over the surface. Next, the magnitude of the acoustic push was inferred by identifying the maximum axial displacement that occurred along the z-axis of the model, see Figure 9.

![Average Values of All Maximum Nodal Displacements for Each Simulation and their Respective Peak Displacements](image)

Figure 9 – An average of all the maximum displacement values was taken for each of the sixteen simulations and plotted above. Peak amplitudes corresponding to each push were also recorded.

Average maximum nodal displacements increase fairly linearly as the axial depth of the focus is increased. The greatest average displacement occurs at a focal depth of 17mm, indicating that this should be the best depth to focus an acoustic push. However, it should be well-noted that the peak nodal displacement declines rapidly as
transducer is focused more deeply into the model due to attenuation. The peak displacement then, curiously, begins to rise for simulations focused at 15, 16 and 17mm. Upon further investigation, it was revealed that peak displacements for these simulations were not occurring at the focus of the acoustic force. Rather, these peaks occurred at 2mm axial depth where constructive interference of axially reflected waves coalesced into a displacement magnitude greater than the original push.

In terms of practicality, the force of an acoustic push should generate the greatest displacement magnitudes in the area of the focus. Reflected waves of greater magnitude than the original push itself will interfere with the ability of the RANSAC post-processing algorithm to accurately calculate shear wave speeds. Therefore, the ability of this method to determine the optimum focal depth for acoustic interrogation of the cervix has been invalidated.

3.2 Maximum Displacements along Axial Depth

Maximum displacements were recorded for each node along the z-axis of the cervix model with the transducer focused at sixteen different focal depths – from 2mm to 17mm. The results have been normalized to a displacement value of 32.5 μm, which occurred at a focal depth of 2mm, see Figure 10.
Figure 10 - Focal depth evaluation performed using a 6MHz impulse transmission frequency. Each curve represents an individual ARFI simulation. Sixteen simulations were performed at focal depths increasing from 2 to 17mm. A single curve indicates the maximum displacement experienced by each node along the axial line of ARFI excitation.

Using this approach, distinct displacement peaks can be seen at focal depths of 4mm up to 11mm. Focal depths preceding 4mm show large displacements occurring at approximately 2.5mm of axial depth and would likely exhibit reflection artifacts in ARFI imaging. The acoustic radiation impulse peaks at focal depths greater than 11mm do not exhibit significant peaks at their respective focuses and are not likely to create high contrast ARFI images. Therefore, it can be concluded from this study that an AcuNav™
transducer operated at these conditions will produce shear waves of greater magnitude and distinction when focused in the range of 5mm-10mm.

**3.3 Frequency Analysis**

Based on the results of Section 3.2 Maximum Displacements along Axial Depth, two more groups of simulations were run – this time at 8MHz and 12MHz – with a more realistic attenuation of 1.3 dB/cm/MHz. The results are shown in Figure 11.

![Figure 11](image)

Figure 11 - Focal depth evaluation performed using 12MHz (top) and 8MHz (bottom) impulse frequencies. Each curve represents an individual ARFI simulation. Sixteen
simulations were performed at focal depths increasing from 2 to 17mm. A single curve indicates the maximum displacement experienced by each node along the axial line of ARFI excitation.

Clear peaks can be seen only up to 5mm of focus depth in the 12MHz case, but can be seen up to 13mm in the 8MHz case. The low displacement amplitudes in the 12MHz simulation are indicative of low contrast ARFI imaging, which would make it difficult to be able to characterize each layer of the cervix, in situ. Normalization value for the 8MHz case was 1.3 times larger than that of the 12MHz case.

Moving forward, it is clear that a transmission frequency of 8MHz will provide the most distinct shear waves using a transducer focused in the range of 5-10mm.

3.4 Material Property Variation

Having identified an optimal focal range of 5-10mm and a desired transmit frequency of 8MHz, the next step was to clarify how material property variation of the cervix layers would affect the ARFI pulse. While exact material properties are still being measured in excised cervical samples by our collaborators at the University of Wisconsin – Madison, we chose several representative stiffness ratios to study in these simulations. The results of these simulations are shown below, see Figure 12.
Figure 12 – Normalized axial displacement profiles in simulated layered cervix with Young’s moduli ranging from 1-10 kPa. The ARFI excitations were either focused at 4 or 12mm. The Young’s moduli of the three cervix layers were modified to determine the effects that heterogeneity has on the displacement response. Layer stiffnesses of the model are listed on the legend in this order: Adjacent to Canal, Central Layer, Outer Surface.

ARFI excitations at 12mm only showed variation when the stiffness of the central layer was increased. Excitations at 4mm showed variation, both, when the stiffness of the inner and central layers were modified. This means, when ARFI excitations are created deeper in the tissue – 12 mm in this case – changing the inner layer’s Young’s modulus has little to no effect on the resulting waveform. However, when ARFI excitations are performed near the 4mm boundary – between the layer adjacent to the canal and the central layer – changes within the central layer will affect how the resulting wave propagates. In both cases, changes in the material properties of the outer layer had no effect on the resulting waveform.
3.5 Shear Wave Speed Tracking

The final consideration of this study was the application of the RANSAC algorithm on simulated data sets with different layer stiffness values. The use of this tool will elucidate whether or not it is feasible to use the AcuNav™ transducer to distinguish between the different layers of the cervix and draw conclusions about material property changes throughout pregnancy.

Unlike the other investigations where the cervix was separated into three fundamentally different anatomical layers, this investigation focuses solely on the central layer, consisting of concentrated collagen and myofibrils, which is expected to undergo the most differentiation.

The first investigation focused on the interrogation of a constant inner layer while the central layer varied in Young’s modulus from 1-10kPa, see Figure 13. Since the ARFI excitation was focused within the inner layer, the RANSAC algorithm was expected to calculate a Young’s modulus of approximately 5kPa for each simulation.
Figure 13 – Young’s moduli calculated by RANSAC algorithm for the inner layer of tissue (E = 5kPa) using two methods: TTP and TTPS. The ARFI excitation was focused at the midpoint of the inner layer (4.5mm axial depth, see left image). The Young’s Modulus of the central layer was varied from 1-10kPa and the outer layer was kept constant (E=5kPa). Since shear wave estimation was performed in the inner layer, the actual Young’s modulus for each simulation should be close to 5kPa.

Although the results appear to vary slightly as the central layer becomes stiffer, the estimates of Young’s modulus for the inner layer are largely consistent.

The second analysis focused an ARFI pulse directly at the boundary between the constant 5kPa inner layer and the varying central layer. The results of this are shown in Figure 14.
In this case, the two RANSAC methods – TTP and TTPS – appear to have a stronger correlation than when interrogating the inner layer. As far as modulus estimation goes, RANSAC seems to calculate shear wave speeds representative of the blend of the two stiffness values being measured. In actual soft tissue there will not be definitive lines between boundaries, however, the results from this test indicate that errors in Young’s modulus estimation can range anywhere from 10-50% when measuring material properties near a boundary.

The third and final model interrogation study was performed at the midpoint of the changing central layer – 9.5mm – and was, by far, the most rewarding, see Figure 15. One can note the decreased accuracy in the RANSAC shear wave speed approximation.
as the Young’s modulus of the central layer is increased; this effect has been quantified in Table 5.

Figure 15 - Young’s moduli calculated by RANSAC algorithm for the central layer of tissue (E= 1-10kPa) using two methods: TTP and TTPS. ARFI excitation was focused at the midpoint of the central layer (9.5mm axial depth, see left image). Young’s Modulus of the inner and outer layers were kept constant (E = 5kPa).

Table 5 – Percent error in the RANSAC calculation of the Young’s modulus of the central layer. Note how the error increases significantly once the central layer exceeds an $E_Y = 5kPa$.

<table>
<thead>
<tr>
<th>Actual $[E_Y]$ (kPa)</th>
<th>1.0</th>
<th>2.0</th>
<th>3.0</th>
<th>4.0</th>
<th>5.0</th>
<th>6.0</th>
<th>7.0</th>
<th>8.0</th>
<th>9.0</th>
<th>10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>RANSAC TTPS Approx. (kPa)</td>
<td>0.99</td>
<td>2.04</td>
<td>3.09</td>
<td>3.93</td>
<td>4.8</td>
<td>5.58</td>
<td>6.36</td>
<td>7.17</td>
<td>7.98</td>
<td>8.79</td>
</tr>
<tr>
<td>Percent Error (%)</td>
<td>-1.0%</td>
<td>2.0%</td>
<td>3.0%</td>
<td>-1.8%</td>
<td>-4.0%</td>
<td>-7.0%</td>
<td>-9.1%</td>
<td>-10.4%</td>
<td>-11.3%</td>
<td>-12.1%</td>
</tr>
</tbody>
</table>

There is a marked increase in RANSAC error as stiffness of the center layer increases. This begs the question. Can the same effect be noted from the previous, inner layer interrogation? The RANSAC error was calculated for the results of the ARFI excitation at 4.5mm, see Table 6.
Table 6 - Percent error in the RANSAC calculation of the Young’s modulus of the inner layer, which was modeled as 5kPa. Note how the error decreases once the central layer exceeds an $E_y = 5kPa$.

<table>
<thead>
<tr>
<th>Central Layer $[E_y]$ (kPa)</th>
<th>1.0</th>
<th>2.0</th>
<th>3.0</th>
<th>4.0</th>
<th>5.0</th>
<th>6.0</th>
<th>7.0</th>
<th>8.0</th>
<th>9.0</th>
<th>10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>RANSAC TTPS Approx. (kPa)</td>
<td>4.56</td>
<td>4.56</td>
<td>4.56</td>
<td>4.56</td>
<td>4.65</td>
<td>4.68</td>
<td>4.71</td>
<td>4.74</td>
<td>4.74</td>
<td>4.74</td>
</tr>
<tr>
<td>Percent Error (%)</td>
<td>-8.8%</td>
<td>-8.8%</td>
<td>-8.8%</td>
<td>-7.0%</td>
<td>-6.4%</td>
<td>-5.8%</td>
<td>-5.2%</td>
<td>-5.2%</td>
<td>-5.2%</td>
<td>-5.2%</td>
</tr>
</tbody>
</table>

These results indicate that shear waves induced in stiffer media can be slowed by adjacent, more compliant media; however, the converse of this statement is not necessarily true. There is no evidence indicating that shear waves propagating in a more compliant medium are sped up by proximity to a stiffer adjacent layer.

To validate that the model itself was not contributing to the error in the shear wave speed approximation at higher and lower Young’s moduli, two more simulations were run. For these two simulations, models were composed of three homogeneous layers; one model had a Young’s modulus of 10kPa for all three layers and the other 1kPa. Shear wave speed approximations based on a 9.5mm ARFI excitation, with the RANSAC TTPS algorithm, calculated the Young’s modulus of the 10kPa and 1kPa models to be 9.45kPa and 0.96kPa, respectively. The respective RANSAC error for each of these two Young’s modulus approximations was -5.5% and -4.0%.

Inlier percentages relate the amount of points used to generate a RANSAC shear wave speed estimation from a given data set. Percentages were found for each of the simulations performed and are shown in Figure 16, Figure 17 and Figure 18.
Figure 16 – Percentage of inliers that composed the RANSAC fitted plane. This plane was used to calculate shear wave speed for an ARFI excitation focused at 4.5mm.

Figure 17 - Percentage of inliers that composed the RANSAC fitted plane. This plane was used to calculate shear wave speed for an ARFI excitation focused at 7.0mm.
Figure 18 - Percentage of inliers that composed the RANSAC fitted plane. This plane was used to calculate shear wave speed for an ARFI excitation focused at 9.5mm.

Note the significant de-correlation that occurs when using the TTP method compared to the TTPS method. Figure 18 also demonstrates a TTPS inlier decrease in the same region that we found more significant RANSAC error for the 9.5mm Young’s modulus estimation.

There are several interesting factors to note here. The first is that the highest correlation between the two methods of shear wave speed tracking occurs when the model is highly homogenous – the central layer stiffness is 5-6kPa. Secondly, one can observe a much larger concentration of outliers associated with the TTP method for heterogeneous models. This de-correlation is likely to be directly related to the estimation technique used in the TTP method.
The TTP method estimates shear wave arrival time by tracking the maximum displacement peak of the wave as it moves across a surface through time. If one considers the shape of the displacement distributions shown in Figure 11, it can be observed that the distribution of displacement is spread over a larger axial range when one excites more deeply into the tissue. This could mean that the maximum displacement TTP picks up may not be directly correlated with the center of the propagating wave, especially in instances where that wave could be deforming due to Young’s modulus variation between layers.

One the other hand, TTPS tracks the greatest slope found on the displacement curve through time. This technique has been shown to be a more viable method for tracking data through a heterogeneous medium than the TTP method, especially with larger beam widths\textsuperscript{[30]}. TTPS is more accurate in this regard because it tracks the leading edge of the wave and is, therefore, less sensitive to changes in the wave shape.
4. Discussion

This analysis sought to answer four key research questions. Answers to these questions are critical in the development of a novel method for identifying cervical insufficiency and susceptibility to preterm birth.

1) What ultrasonic focal configuration should be used to achieve the greatest ARFI imaging contrast?

2) After identifying an optimum focal range, what ultrasonic transmit frequency will likely provide the best ARFI imaging result?

3) What effect does material property variation within the layers of the cervix have on ARFI impulses?

4) Using ARFI imaging algorithms currently used in vivo, is it possible to extract independent layer material property values?

In identifying the optimal focal configuration for the AcuNav™, there were several key considerations. Firstly, a methodology had to be established that could quantify and evaluate the differences between acoustic radiation excitations that were focused at different axial depths. This was surprisingly, non-trivial. After the failure of the lateral-axial surface evaluation to reveal any tangible or valid results, the decision was made to simplify the evaluation technique and only look at nodes that lay directly in line with the acoustic radiation push.
The simplified approach provided a much more comprehensive analysis. Focal depths within the 5-10mm range showed a bell-shaped maximum displacement peak that would provide increased ARFI contrast in the ROI and an evenly distributed shear wave within the cervix. In contrast, the focal range between 2 and 4mm exhibited large, shear wave reflection induced displacements near the os of the cervix model that would likely give rise to artifacts in ARFI images. Excitations generated in the focal range of 11 to 17mm showed a limited peak that was not well differentiated along the axial depth.

A limiting factor in the methodology used for this focal depth analysis was the maintenance of a constant aperture size. When focal depth is increased and the aperture size is maintained, the F/# of the acoustic field increases. A large F/# corresponds to a wider beam and a larger, more uniform depth of field. A larger and straighter depth of field creates a more uniform shear wave; however, the amplitude of the resulting shear wave is lower than that of a wave generated by a pulse with a lower F/#. For this part of the analysis, it was assumed that by transmitting with all of the available elements on the AcuNav™, the highest possible maximum displacements could be achieved. It was assumed that this would provide for the greatest signal to noise ratio and make the induced shear wave easier to track.

Evaluating which transmit frequency to use was an exceedingly simpler task than finding an optimal focal range. Plots of the 6, 8 and 12MHz cases indicated that an 8MHz transmit frequency provided for sharper, more defined maximum displacement
peaks. These more clearly defined peaks would create shear waves localized in the ROI, reducing the effect of reflecting wave artifacts, while maximizing ARFI imaging contrast.

As the exact mechanisms of in vivo cervical ripening are still largely unknown, it was necessary to evaluate what effect non-uniform, anatomical layer differentiation would have on the proposed imaging technique. The two focal zones considered in the material property variation analysis represented the extremes of the optimized focal range study. Focusing near the canal/central boundary resulted in ARFI impulse variation, both, when the inner layer and central layer material properties were varied. Interestingly enough, focusing the transducer deeper into the central layer was found to eliminate any artifacts caused by a differentiating inner layer. Granted, extreme material property differentiation was not considered in this analysis, it was made clear that creating an acoustic impulse distal from the canal/central boundary, yet within our previously defined focal range, would yield the best imaging results.

The fourth phase of this investigation proved to be the most fruitful, in that it provided a topic of further research – shear wave lagging. It is well known throughout the ultrasound and physics community that shear waves propagating through an isotropic medium will travel at a speed proportional to the material properties of that medium. This principle was introduced earlier in the study as being governed by the following equation:
\[ c_T = \sqrt{\frac{\mu}{\rho}} : \mu = \frac{E}{2(1+\nu)} \]

Where: \( c_T \) – shear wave speed [m/s], \( \mu \) - shear modulus [Pa], \( \rho \) – density of medium [kg/m^3], \( E \) – Young’s modulus [Pa], \( \nu \) – Poisson’s ratio

This relationship results in uneven shear wave propagation in a medium composed of layers with different Young’s moduli, see Figure 19.

**Figure 19** – Shear wave propagating through layered cervix model develops an angled trajectory associated with the material variation between isotropic layers. In this case the central layer had a Young’s modulus of 1kPa and the inner layer had a Young’s modulus of 5kPa.

In this study, it was observed that shear waves generated in a stiff region were slowed as a result of being adjacent to a more compliant region. This is likely the result of one or both or the following conclusions: either, the more compliant medium disperses strain energy away from the stiffer medium or, in order to maintain
displacement continuity at the material boundary, wave propagation in the stiffer medium retards.

Given the observed results of this study, it would be prudent to develop a correction factor for the quantification of stiffer regions near compliant regions. This correction factor would be a function of the stiffer region’s proximity to a compliant region and the perceived difference between the stiffer region and the more compliant region.

It can be concluded that the proposed technique for cervical evaluation can feasibly detect changes in cervix material properties throughout the course of pregnancy, given that the cervix exhibits a relatively isotropic material nature. More promising, this technique can be used to evaluate the material property changes within the different layers of the cervix as the pregnancy progresses. However, these conclusions are made with some hesitation as the cervix exhibits known anisotropy preferential to the direction of its collagen structure.

As a result, future studies will focus on the effects that transversely isotropic material property definitions have on RANSAC shear wave estimations. This analysis will further clarify the feasibility of this approach to classify cervical material properties and aid our clinical collaborators in further refining their testing methods.

This study has shown the utility of using the finite element method as an optimization tool for experimental ultrasonic imaging techniques. In situations where
clinical testing is a requirement for methodology validation, it is important to have a refined technique prior to starting the study. This will not only save a significant amount of time, but will serve to reduce the number of clinical trials necessary before significant headway can be made in the study.
References


