Inferring Micro-Architecture from the Ultrasonic Attenuation in Cortical Bone

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Abstract

In this work we propose a power law model to describe the attenuation of ultrasonic waves in cortical bone. We use data generated using a finite-difference, time domain (FDTD) numerical simulation. We fit this phenomenological model to the simulated data by optimizing parameters under an ordinary least squares (OLS) framework. Local sensitivity analysis is then performed on the resulting parameter estimates in order to determine to which estimates the model is most sensitive. We find that the sensitivity of the model to various parameter estimates depends on the micro-architectural parameters, pore diameter ($\phi$) and pore density ($\rho$). In order to get a sense for how confidently we are able to estimate model parameters, we calculate 95% confidence intervals for these estimates. In doing so, we establish the ability to estimate model-sensitive parameters with a high degree of confidence. Being able to accurately estimate model parameters from which we hope to infer micro-architectural ones, will allow us to determine pore density and diameter via an inverse problem given real or simulated ultrasonic data.

1 Introduction

Osteoporosis changes the micro-structure of both cortical and trabecular bone [7, 23] which leads to fragility fractures [20, 18], higher morbidity and mortality, and reduction of life expectancy by 1.8 years [6]. Because it constitutes 80 percent of the human skeleton [17], cortical bone supports the main load of the body and largely contributes to the skeletal mechanical competence. The micro-architecture of cortical porosity impacts the macroscopic mechanical properties of cortical bone, and is affected by osteoporosis. It is therefore highly relevant to develop methods for the quantitative assessment of the micro-architecture of cortical porosity, and we hypothesize that tracking the micro-structural changes in cortical bone could benefit the early stage diagnosis of osteoporosis and may enable treatment monitoring. High resolution X-ray CT and MRI based techniques can be used for the characterization of bone, but MR lacks resolution, and CT based methods are ionizing [5, 22]. Both methods have limitations associated with cost and availability of the scanners. Quantitative ultrasonic techniques have the advantage of being relatively low cost and widely available. Additionally, the mechanical nature of ultrasonic waves makes them sensitive to micro- and macro-mechanical changes of cortical bone. The correlation between micro-architectural and ultrasonic...
parameters could be a key factor for the ultrasonic characterization of the micro-architecture of cortical bone.

A number of studies have been conducted to address the micro-architectural properties of bone using ultrasonic parameters. Most of them have been applied to the assessment of trabecular bone [3, 9, 12, 11, 15, 16]. The interaction between ultrasonic waves and the micro-architecture of cortical bone has not been investigated as thoroughly as it has been for trabecular bone. Various techniques have been developed to quantify cortical thickness [13, 14, 8] and speed of sound in cortical bone [4, 12], which is related to the Young’s modulus under some conditions. Mandarano-Fiho et al., [10] carried out an experimental study in vitro to evaluate the influence of cortical bone thickness on ultrasound wave velocity. Sievanen et al., [19] investigated the association between speed of sound and cortical density, cortical wall thickness, and the total cortical area. Among all ultrasonic parameters, ultrasonic attenuation, and its frequency dependence have been investigated the least. In a study by Zheng [25], the spectral ratio method was extended to estimate the broadband ultrasound attenuation (BUA) in cortical bone in axial transmission using the primary and multiple reflections between the material interfaces.

To support the aforementioned studies, and to enable a deeper understanding of what is measured when ultrasound propagates in cortical bone, an appropriate model describing the behavior of attenuation in cortical microstructures remains to be proposed. Ideally, such a model would establish relationships between ultrasonic attenuation and its frequency dependence and micro-architectural parameters of cortical porosity, which could include pore diameter and density. This would ultimately enable one to solve inverse problems in order to infer microstructural properties of cortical porosity from ultrasound measurements. The present study focuses on pore diameter and pore density, which are known to be modified by osteoporosis [7, 23]. However, the individual and independent effect of these two parameters on ultrasonic attenuation is still unclear.

In this study we use finite differences numerical simulations to measure the attenuation and its frequency dependence in slabs of porous media simulating simplified versions of cortical bone. Pore density and pore diameter are modified independently and ultrasound attenuation is measured for a range of frequencies going from 1 to 8 MHz. A simple power law model as was proposed in [24] is assumed to describe the behaviour of the attenuation as a function of frequency. The model parameter estimates are observed to change significantly and monotonously with pore density and pore diameter. The relative sensitivity of all model parameters is studied. This work is the first step toward the development of the solution to an inverse problem that would allow one to retrieve cortical pore density and average pore diameter from ultrasonic measurements in cortical bone.

In Section 2 we provide the methodology for the numerical simulations that generate the data. The mathematical and statistical models, which are used to fit this data, are given in Section 3. Section 4 details the standard error methodology and provides the sensitivity equations for the power law model. The results of this work are given in Section 5, and a discussion follows in Section 6.

2 Methodology for Data Collection

2.1 Simulation Framework

The finite-difference, time domain (FDTD) SimSonic research freeware (www.simsonic.fr) [4], which can simulate elastic waves propagating in heterogeneous media with finely controlled mechanical
and architectural properties, is used to simulate wave propagation in media resembling cortical bone. The media are constituted of solid slabs containing a distribution of fluid-filled pores. The solid phase is given the material properties of pure bone and the fluid those of water. The independently tuneable material properties can be defined at all points in space, which enables a deep understanding of their specific individual effect. The bone geometry is generated using a Monte Carlo method for a given pore density and pore size. Pores are randomly distributed in the solid bone matrix until the required pore density is reached. The pore density and diameter ranges are respectively chosen as $[3, 16]$ pore/mm$^2$ and $[20, 100]$ µm [21].

The spectroscopy is performed in 1-8 MHz range with 0.5 MHz frequency interval. A plane wave constituted by a Gaussian ultrasonic pulse with a central frequency within the spectroscopy range and -6dB bandwidth of 20 percent is transmitted through the medium. Figure 1 illustrates an example of a medium geometry and the emitted pulse. The slab dimensions are 10mm by 10mm.

Table 1 summarizes the material properties used in the simulations.

<table>
<thead>
<tr>
<th>Solid Properties</th>
<th>Value</th>
<th>Fluid Properties</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wave speed: $C_b$</td>
<td>$4 \text{ mm}/\mu\text{s}$</td>
<td>Wave speed: $C_w$</td>
<td>$1.54 \text{ mm}/\mu\text{s}$</td>
</tr>
<tr>
<td>Density: $\rho_b$</td>
<td>$1.85 \text{ g}/\text{ml}$</td>
<td>Density: $\rho_w$</td>
<td>$1.00 \text{ g}/\text{ml}$</td>
</tr>
<tr>
<td>$C_{11}$</td>
<td>$29.60 \text{ GPa}$</td>
<td>$C_{11}$</td>
<td>$2.37 \text{ GPa}$</td>
</tr>
<tr>
<td>$C_{22}$</td>
<td>$29.60 \text{ GPa}$</td>
<td>$C_{22}$</td>
<td>$2.37 \text{ GPa}$</td>
</tr>
<tr>
<td>$C_{12}$</td>
<td>$17.60 \text{ GPa}$</td>
<td>$C_{12}$</td>
<td>$2.37 \text{ GPa}$</td>
</tr>
<tr>
<td>$C_{66}$</td>
<td>$6.00 \text{ GPa}$</td>
<td>$C_{66}$</td>
<td>$0.00 \text{ GPa}$</td>
</tr>
</tbody>
</table>

Table 1: Material properties of the solid and fluid phases [4]

Figure 1: Input signal and schematic bone geometry; Pore size: $100$ µm; Pore Density: 5 pore/mm$^2$

In all simulations, Perfectly Matched Layer (PML) boundary conditions are applied at both ends of the geometry in the direction of wave propagation with the thickness of 15 times that of wavelength so that the effect of reflections at the ends of the slab can be ignored. Symmetry boundary conditions are chosen in the direction perpendicular to the direction of wave propagation so that the effect of diffraction can be avoided, and plane wave conditions are assumed. Simulations are run in 2D and the grid step is selected as $10\mu\text{m}$ in both directions, enabling a spatial sampling of over 50 points.
per wavelength.

2.2 Attenuation Measurement: Time-Distance Matrix Approach (TDMA)

SimSonic is used to transmit plane waves through the porous cortical bone medium described above. The propagated signals are recorded at 30 consecutive longitudinal positions along the sample in the direction of wave propagation.

The time-domain recorded signals are stored in a time-distance matrix, \( s(\bar{t}, x) \). The matrix can be converted into the frequency domain, \( S(\omega, x) \) through Fast Fourier Transform (FFT). Hence, each element in the frequency-distance matrix, \( S(\omega, x) \) represents the spectrum at a given position.

By assuming an exponential decay for the propagated signal through a bone sample [12], the amplitude of the signals contained in the frequency-distance matrix can be approximated as:

\[
|S(\omega, x)| = e^{-\alpha(\omega)x}.
\]

Hence, for each frequency if \( \ln|S(\omega, x)| \) versus \( x \) is plotted, the absolute value for the slope of the linear fit to the data represents the attenuation coefficient, \( \alpha(\omega) \). As an example, Figure 2 depicts the attenuation spectroscopy in 1-8 MHz frequency range for pore diameter: 100 \( \mu m \) and pore density: 5 \( pore/mm^2 \).

![Figure 2: Attenuation spectroscopy](image)
Pore size: 100 \( \mu m \), Pore density: 5 \( pore/mm^2 \)

3 Mathematical and Statistical Model

Mathematical models are used to represent physical and biological systems in order to investigate hypothesis regarding the underlying physical process. A mechanistic model hypothesizes the relationships between physically interpretable parameters and variables, while a phenomenological model captures the qualitative trends of the desired dynamics. Here, the physical process of interest is wave propagation in bone. We begin by developing a phenomenological model that describes the
trends seen in numerical simulation for the attenuation in cortical bone as a function of ultrasonic wave frequency. This mathematical model is given by

\[ \alpha(f) = af^b + c, \]  

(2)

where \( \alpha \) represents the attenuation coefficient, which is dependent on frequency, \( f \). The model parameters are given by \( \theta = [a \ b \ c] \).

In order to make meaningful inferences regarding parameter estimates, one must also take into account error incurred in the data collection process. One does so by specifying a statistical model, which represents the observation process regarding data collection. In order to account for the uncertainty we would expect in observational data, we consider the following statistical error model

\[ Y(f) = \alpha(f, \theta_0) + \mathcal{E}(f), \]  

(3)

where \( Y(f) \) is a random variable, \( \theta_0 \) is the nominal parameter vector, and the \( \mathcal{E} \) are assumed to be independent and identically distributed with mean 0 and variance \( \sigma_0^2 \). A realization of this statistical error model is given by

\[ y(f) = \alpha(f, \theta_0) + \epsilon(f), \quad f \in [f_0, f_F], \]  

(4)

where \( \epsilon \) is a specific realization of the random variable \( \mathcal{E} \). This is a reasonable specification of the statistical error model since the numerical simulation that generates the data likely allots the same error to each data point. It is important to note that both the mathematical and statistical model need to be correctly specified in order to make meaningful inferences regarding parameter estimates.

4 Sensitivity and Standard Error Methodology

Since we assume an absolute error statistical model, given in (4), we estimate the model parameters by solving an inverse problem with an ordinary least squares (OLS) formulation, following [1, 2]. Solving this inverse problem corresponds to minimizing the sum of squared errors between the data and the model output when we treat all observations as equally important.

The OLS estimator is given by

\[ \Theta_{OLS} = \Theta_{OLS}^N = \text{argmin}_\theta \sum_{j=1}^N [Y_j - \alpha(f_j, \theta)]^2, \]  

(5)

where \( Y_j \) is a random variable corresponding to the observation process and \( N \) represents the number of frequency points. A realization of the random variable, \( \Theta_{OLS} \), is given by

\[ \hat{\theta}_{OLS} = \hat{\theta}_{OLS}^N = \text{argmin}_\theta \sum_{j=1}^N [y_j - \alpha(f_j, \theta)]^2, \]  

(6)

where \( y_j \) is realization of \( Y_j \). With the parameter estimate, \( \hat{\theta} \) (where we now suppress the dependence of the estimate on the OLS formulation), we can compute the sensitivity matrix as

\[ \chi_{j,k} = \frac{\partial \alpha(f_j, \theta)}{\partial \theta_k}, \quad j = 1, \ldots, N, \quad k = 1, \ldots, p, \]  

(7)
where \( p \) represents the number of model parameters. Specifically, since the model given in (2) can be explicitly differentiated with respect to the parameters, we have that

\[
\frac{\partial \alpha(f_j, \hat{\theta})}{\partial a} = f_j^b, \\
\frac{\partial \alpha(f_j, \hat{\theta})}{\partial b} = a \log(f_j)f_j^b, \\
\frac{\partial \alpha(f_j, \hat{\theta})}{\partial c} = 1, \quad j = 1, \ldots, N.
\] (8)

(9)

(10)

Notice that \( \chi = \chi^N \in \mathbb{R}^{N \times p} \) is dependent on the number of frequency points as well as the parameter estimate, \( \theta = [\hat{a} \quad \hat{b} \quad \hat{c}] \). The true, constant variance is a random variable given by

\[
\sigma_0^2 = \frac{1}{N} E \left[ \sum_{j=1}^{N} [Y_j - f(t_j, \theta_0)]^2 \right],
\] (11)

which is estimated, adjusting for the bias, by

\[
\hat{\sigma}^2 = \frac{1}{N - p} \left[ \sum_{j=1}^{N} [y_j - f(t_j, \hat{\theta})]^2 \right].
\] (12)

We can then estimate the covariance matrix as

\[
\hat{\Sigma}^N = \hat{\sigma}^2 [\chi^T(\hat{\theta})\chi(\hat{\theta})]^{-1}.
\] (13)

Then, the asymptotic standard errors are given as

\[
SE_k(\theta_0) = \sqrt{(\Sigma_0^N)_{kk}}, \quad k = 1, \ldots, p,
\] (14)

which are estimated by

\[
SE_k(\hat{\theta}) = \sqrt{(\hat{\Sigma}^N(\hat{\theta}))_{kk}}, \quad k = 1, \ldots, p.
\] (15)

The confidence interval for parameter estimate \( \hat{\theta}_k \) with a confidence level of \( 100(1 - \alpha)\% \), is given by

\[
[\hat{\theta}_k - t_{1-\alpha/2}SE_k(\hat{\theta}), \hat{\theta}_k + t_{1-\alpha/2}SE_k(\hat{\theta})],
\] (16)

where \( \alpha \in [0,1] \) and \( t_{1-\alpha/2} \) is computed from the Student’s \( t \) distribution with \( N - p \) degrees of freedom.

5 Results and Discussion

The model parameter estimates (\( \hat{\theta} = [\hat{a} \quad \hat{b} \quad \hat{c}] \)) versus pore diameter (\( \phi \)) and pore density (\( \rho \)) are given in Figures 3 - 5. From these figures we see that there is a consistent trend relating the parameter estimates to pore diameter and density. For instance, Figures 3 and 5 show that for all densities and diameters \( \leq 60 \mu m \) the estimates for \( a \) and \( c \) are constant. Then, as diameter increases, the estimates for \( a \) increase while the estimates for \( c \) decrease. Similarly, in Figure 4 we see a somewhat linear relationship between the estimates for \( b \) and the pore diameter, where the
estimates increase as diameter decreases. From this we gather how it may be possible to infer pore diameter and density from the estimates of the model parameters.

Figure 3: Parameter $a$ estimates versus pore diameter ([20 40 60 80 100] µm) and pore density ([3 5 6 7 8 10 12 14 15 16] pore/mm$^2$).

Figure 4: Parameter $b$ estimates versus pore diameter ([20 40 60 80 100] µm) and pore density ([3 5 6 7 8 10 12 14 15 16] pore/mm$^2$).
Since our goal is to infer micro-architectural information from these parameter estimates, we wish to determine which parameters have the most significant influence on the model solution. To do so, we use local sensitivity analysis to examine how the model output changes with respect to perturbations in the nominal parameter estimates for a given data set. That is, we use the methodology laid out in Section 4 to estimate model parameters for data sets corresponding to pore diameters [20 40 60 80 100] \( \mu m \), and pore densities [3 5 6 7 8 10 12 14 15 16] pore/mm\(^2\). We then calculate the sensitivity of the model with respect to these estimates using Equations (8)-(10). These sensitivities are plotted versus frequency (MHz) and given in Figures 6, 10, 14, 19, and 23. Note that the parameter estimates themselves are given in the legend. For a more convenient comparison, the sensitivities of the estimates for \( a \) have been plotted versus all densities and frequencies in Figures 7, 11, 15, 20, and 24. Similarly, the estimates for \( b \) versus density and frequency are given in Figures 8, 12, 16, 21, and 25.

The parameter estimates and corresponding 95% confidence intervals are given in Figures 9, 13, 17, 22, and 26. For comparison, 80% confidence intervals are given for pore diameter 60\( \mu m \) in Figure 18.
5.0.1 Diameter 20 µm
Figure 6: Local model sensitivity to parameter estimates for pore diameter 20\(\mu m\), densities of [3 5 6 7 8 10 12 14 15 16] pore/mm\(^2\), and frequency 1-8 MHz.
Figure 7: Local sensitivity to $\hat{a}$ for pore diameter $20\mu m$, densities of $[3 5 6 7 8 10 12 14 15 16]$ pore/mm$^2$, and frequency 1-8 MHz.

Figure 8: Local sensitivity to $\hat{b}$ for pore diameter $20\mu m$, densities of $[3 5 6 7 8 10 12 14 15 16]$ pore/mm$^2$, and frequency 1-8 MHz.
Figure 9: Parameter estimates and corresponding 95% confidence intervals for $\hat{a}$, $\hat{b}$, and $\hat{c}$ for pore diameter 20$\mu$m and densities of [3 5 6 7 8 10 12 14 15 16] pore/mm$^2$.

5.0.2 Diameter 40$\mu$m
Figure 10: Local model sensitivity to parameter estimates for pore diameter 40 $\mu$m, densities of [3 5 6 7 8 10 12 14 15 16] pore/mm$^2$, and frequency 1-8 MHz.

Figure 11: Local sensitivity to $\hat{a}$ for pore diameter 40 $\mu$m, densities of [3 5 6 7 8 10 12 14 15 16] pore/mm$^2$, and frequency 1-8 MHz.
Figure 12: Local sensitivity to $\hat{b}$ for pore diameter 40$\mu m$, densities of [3 5 6 7 8 10 12 14 15 16] pore/mm$^2$, and frequency 1-8 MHz.
Figure 13: Parameter estimates and corresponding 95% confidence intervals for \( \hat{a}, \hat{b}, \) and \( \hat{c} \) for pore diameter 40\( \mu m \) and densities of \([3 5 6 7 8 10 12 14 15 16]\) pore/mm\(^2\).

### 5.0.3 Diameter 60µm

![Sensitivity plots for density 3, 5, 6 pore/mm\(^2\) and diameter 60µm](image)
Figure 14: Local model sensitivity to parameter estimates for pore diameter 60\(\mu m\), densities of \([3\ 5\ 6\ 7\ 8\ 10\ 12\ 14\ 15\ 16]\) pore/mm\(^2\), and frequency 1-8 MHz.
Figure 15: Local sensitivity to $\hat{a}$ for pore diameter 60$\mu$m, densities of [3 5 6 7 8 10 12 14 15 16] pore/mm$^2$, and frequency 1-8 MHz.

Figure 16: Local sensitivity to $\hat{b}$ for pore diameter 60$\mu$m, densities of [3 5 6 7 8 10 12 14 15 16] pore/mm$^2$, and frequency 1-8 MHz.
Figure 17: Parameter estimates and corresponding 95% confidence intervals for $\hat{a}$, $\hat{b}$, and $\hat{c}$ for pore diameter 60$\mu$m and densities of [3 5 6 7 8 10 12 14 15 16] pore/mm$^2$. 
Figure 18: Parameter estimates and corresponding 80% confidence intervals for $\hat{a}$, $\hat{b}$, and $\hat{c}$ for pore diameter 60\(\mu m\) and densities of \([3 5 6 7 8 10 12 14 15 16]\) pore/mm\(^2\).

5.0.4 Diameter 80\(\mu m\)
Figure 19: Local model sensitivity to parameter estimates for pore diameter 80\( \mu \text{m} \), densities of \([3\ 5\ 6\ 7\ 8\ 10\ 12\ 14\ 15\ 16]\) pore/mm\(^2\), and frequency 1-8 MHz.
Figure 20: Local sensitivity to \( \hat{a} \) for pore diameter 80\( \mu m \), densities of [3 5 6 7 8 10 12 14 15 16] pore/mm\(^2\), and frequency 1-8 MHz.

Figure 21: Local sensitivity to \( \hat{b} \) for pore diameter 80\( \mu m \), densities of [3 5 6 7 8 10 12 14 15 16] pore/mm\(^2\), and frequency 1-8 MHz.
Figure 22: Parameter estimates and corresponding 95% confidence intervals for $\hat{a}$, $\hat{b}$, and $\hat{c}$ for pore diameter $60\mu m$ and densities of $[3 5 6 7 8 10 12 14 15 16]$ pore/mm$^2$.

5.0.5 Diameter $100\mu m$
Figure 23: Local model sensitivity to parameter estimates for pore diameter 100\(\mu m\), densities of [3 5 6 7 8 10 12 14 15 16] pore/mm\(^2\), and frequency 1-8 MHz.

Figure 24: Local sensitivity to \(\hat{a}\) for pore diameter 100\(\mu m\), densities of [3 5 6 7 8 10 12 14 15 16] pore/mm\(^2\), and frequency 1-8 MHz.
Figure 25: Local sensitivity to $\hat{b}$ for pore diameter 100μm, densities of [3 5 6 7 8 10 12 14 15 16] pore/mm², and frequency 1-8 MHz.
Figure 26: Parameter estimates and corresponding 95% confidence intervals for \( \hat{a}, \hat{b}, \) and \( \hat{c} \) for pore diameter 100\( \mu \)m and densities of [3 5 6 7 8 10 12 14 15 16] pore/mm\(^2\).

Notice that the sensitivity of the model with respect to estimates of \( \hat{c} \) (denoted \( \hat{c} \)) will be constant and equal to 1 from Equation (10). Furthermore, we see from the sensitivity figures that as frequency increases, so does the sensitivity of the model with respect to the estimates of \( a \) and \( b \) (denoted \( \hat{a} \) and \( \hat{b} \) respectively). This intuitively makes sense in looking at Equations (8) and (9) as both are increasing functions of frequency.

We then observe that model sensitivity to \( \hat{a} \) and \( \hat{b} \) depends heavily on pore diameter. There is a general trend that for smaller diameters (\( \phi = 20\mu m \) and \( \phi = 40\mu m \)), the model is sensitive only to \( \hat{a} \), which is seen in Figures 6 and 10. Similarly, from Figure 19, we see that the model is sensitive only to \( \hat{b} \) for larger diameters (\( \phi = 100\mu m \)). For intermediate pore diameters (\( \phi = 60\mu m \) and \( \phi = 80\mu m \)), model sensitivity to \( \hat{a} \) and \( \hat{b} \) depends on pore density. For instance, from Figure 14 we see that for \( \phi = 60\mu m \) at low densities (3 and 5 pore/mm\(^2\)) the model is sensitive to \( \hat{a} \). However, as density increases, model sensitivity to \( \hat{b} \) increases while sensitivity to \( \hat{a} \) decreases. For higher densities (\( \geq 14 \) pore/mm\(^2\)) model sensitivity to \( \hat{a} \) and \( \hat{b} \) are roughly the same. A similar trend is seen in Figure 19 for \( \phi = 80\mu m \), except here the model is only slightly more sensitive to \( \hat{a} \) as \( \hat{b} \) for density 3 pore/mm\(^2\). As density increases, sensitivity to \( \hat{a} \) decreases while sensitivity to \( \hat{b} \) increases. For high densities (\( \geq 14 \) pore/mm\(^2\)) the model is only sensitive to \( \hat{b} \).

Next, we address the confidence interval figures. In general, the size of the confidence intervals depends on the level of confidence desired, the parameter estimates themselves, and the relative sensitivity of the model to these estimates. Notice that relative to parameter estimate size, the confidence intervals for \( \hat{c} \) are significantly larger than for \( \hat{a} \) and \( \hat{b} \) for all diameters and densities. This is due to the fact that the model is not sensitive to \( \hat{c} \), which makes difficult estimating this parameter with high confidence. Furthermore, we found there is not a strictly monotone trend in confidence interval width with respect to increasing density and diameter. This is due to the standard errors (and resulting confidence interval widths (see Section 4)) dependence on multiple factors. We do, however, note that it is common for the confidence intervals for all estimates to widen as density increases (e.g., see Figures 13 and 22). This could be an artifact of the numerical simulation that results in the data from which the parameter estimates are derived. For one, multiple geometries corresponding to a fixed pore density and diameter are not considered. Furthermore, as pore density increases the scattering regime changes as more multiple scattering occurs. This affects the parameters estimated when fitting the power law model to data for these higher densities.
Since 95% confidence in parameter estimates may be higher than the acceptable level of confidence, 80% confidence intervals have been given for pore diameter 60µm (see Figures 17 and 18). As we would expect, the intervals are significantly wider when 95% confidence is desired. Furthermore, we still see the trend of wider intervals at higher densities in these figures.

6 Conclusions

The overall goal of this research was to establish that it is possible to infer micro-architectural properties such as pore density and pore diameter of cortical bone from ultrasound data. In order to do this, we developed a phenomenological model that describes the attenuation of ultrasonic waves in cortical bone. We numerically generated data using a finite-difference, time domain SimSonic research freeware, which simulates elastic waves propagating in heterogeneous media. We then fit this model to the simulated data using an ordinary least squares framework for the inverse problem. With the resulting estimates, we performed local sensitivity analysis and calculated confidence intervals for the parameters estimated.

We determined that model sensitivity to parameter estimates depends on pore diameter and density. Namely, we determined via the analytical partial derivatives that the model is not sensitive to $c$. Furthermore, for small diameters ($\phi = 20\mu m$ and $\phi = 40\mu m$) the model is sensitive mainly to estimates of $a$; whereas for large diameters, ($\phi = 100\mu m$) the model is sensitive mainly to estimates of $b$. For intermediate diameters ($\phi = 60\mu m$ and $\phi = 80\mu m$) sensitivity depends on pore density, where the model is more sensitive to $\hat{a}$ at low densities and more sensitive to $\hat{b}$ at high densities. We also calculated asymptotic standard errors and confidence intervals for the parameter estimates in order to determine for what diameters and densities we can accurately estimate the model parameters. We found that for parameter estimates the model was sensitive to ($a$ and $b$) we could estimate parameters with a high level of confidence. In general, the 95% confidence intervals for these estimates were wider at high densities ($\geq 14$ pore/mm$^2$).

Establishing that we can accurately and confidently estimate the parameters for the power law model allows us to address the next goal of relating the model parameters to the micro-architectural ones. In Figures 3 - 5 we see that there is a clear dependence of parameter estimates on diameter and density. Furthermore, we have established that there exist density and diameter ranges for which our model is more or less sensitive to certain parameters. With this we could propose a model as follows

$$\alpha(f) = a(\phi, \rho)f^{b(\phi, \rho)} + c,$$

where the sensitive model parameters ($a$ and $b$) are themselves a function of the micro-architectural ones. With a model of this form, one could infer pore diameter ($\phi$) and density ($\rho$) from the estimates of $a$ and $b$. In future work we also plan to verify these results, which used simulated data, with data taken from human cortical bone samples.

The model developed and analyzed in this study was based on 2D numerical simulation mimicking the wave propagation within the cortical bone. Unlike the experimental study, these set of simulations enabled the independent control over the micro-structural parameters such as pore diameter and pore density. The absorption was not considered in the simulations and the developed model. In other words, the attenuation considered in this work was exclusively due to the wave scattering. The effect of absorption on the simulation and the model should be addressed in future studies. The
validity of 2D assumption in the simulations also need to be addressed by comparing the results with 3D simulations.

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