QUANTITATIVE ULTRASOUND IMAGING OF IN VIVO BREAST TUMORS

by

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Abstract

The main goal of this dissertation is to perform quantitative ultrasound imaging (QUS) of in vivo breast tumors in order to provide new tools to differentiate benign from malignant breast masses. The studies outlined in Chapters 3-4 demonstrate that attenuation and backscatter coefficients (BSC) of phantoms can be estimated from the radiofrequency echo data acquired by a clinical ultrasound imaging system, when a well-calibrated reference phantom is used to account for dependencies of echo signals on system settings and transducer properties. Chapter 5 presents attenuation coefficients and backscatter coefficients for an animal breast tumor model and demonstrates the feasibility of producing accurate QUS parameters regardless of imaging system used. The study in Chapter 5 was validated in Chapter 6 using a phantom that mimics scanning conditions encountered in the animal model study. A least squares method (LSM) for simultaneous attenuation and backscatter coefficient estimation was introduced to account for attenuation over inhomogeneous paths between an ultrasound transducer and region of interest within a mass. The LSM was verified using well-characterized phantoms. Later the LSM was applied in QUS studies of human breast masses. Preliminary data on attenuation coefficients, BSCs, and effective scatterer diameters (ESD) within human breast masses were derived from a subject population undergoing breast biopsy procedures. The total attenuation in the mass was estimated from the product of the attenuation coefficient and antero-posterior (AP) dimension and was compared to relative acoustic shadowing criteria reported as “posterior echo features” in the ultrasound breast imaging BI-RADS lexicon. The BSC averaged over frequency (ABSC) provides information of the average scattering strength (“echogenicity”) of an object. The ABSC
was compared to the “echo pattern” descriptor of the BI-RADS descriptors and showed a potential to quantify the echogenicity within masses. A scatter plot of the ABSC and attenuation coefficient showed potential to differentiate between fibroadenomas and carcinomas with a simple linear discriminant. In addition, most human fibroadenomas exhibited a wider distribution of ESD estimates over the ROI than carcinomas. Chapter 9 presents an assessment of accuracy of attenuation measurements by the reference phantom method (RPM) when the tissue sound speed differs from that of the reference. The RPM is convenient for accounting for system factors on echo data. However the speeds of sound in the tissue and reference need to be the same for this method to be most effective. The study also discusses the methods to minimize errors.

These results demonstrate that a great deal of progress has been made in the effort to develop QUS technology to improve breast ultrasound specificity. This thesis also demonstrates that, even with the demonstrated potential provided here, there is more that can be done to significantly improve the state of the art in QUS technology.
I am grateful to my advisors, Drs. Timothy Hall and James Zagzebski for all their help and support in finishing this work. They encouraged me to keep forward and cheered me up with their warmth. They were also my life supervisors. I would also like to thank Dr. Sethares. I still remember the conversation we had in front of Engineering Hall long time ago. Without that conversation, I could have lived a different life by now. He always encouraged me to enjoy my life and feel happy.

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Chapter 1: Introduction

Breast cancer is the second most common cancer among women and the second leading cause of cancer death in women in the United States.\(^1\) Currently, the common screening tests for breast cancer are clinical breast exams, breast self-exams, and mammography. While clinical and self breast exams have not been found to decrease the risk of dying from breast cancer,\(^2\) periodic mammograms of age-appropriate, asymptomatic women have been shown to decrease breast cancer mortality.\(^3\)\(^-\)\(^5\) The American Cancer Society recommends annual mammograms for women of age 40 and over, and mammographic screening should continue as long as women are in good health. For women, with a family history of breast cancer, a genetic predisposition, or certain other risk factors,\(^6\) magnetic resonance imaging (MRI) is recommended in addition to mammograms. In several studies,\(^7\)\(^-\)\(^12\) MRI has provided good sensitivity in screening for breast cancer in women at high risk based on family history. However, not all women are good candidates for MRI (claustrophobia, metal implants, etc.), and MRI is not uniformly available (MRI systems are rare in rural areas), so an alternative imaging modality for breast imaging is ultrasound. Ultrasound imaging is not recommended as a sole screening tool since it has a high false-positive rates.\(^13\)\(^,\)\(^14\) However, several studies have reported that ultrasound screening in women with dense breasts and negative mammograms has increased the cancer detection rate from 2.8 to 4.6 cancers per 1,000 women.\(^15\)\(^-\)\(^20\) Further, mammography performs poorly for cancer detection in women with dense breasts; the conspicuity of tumors, calcifications, and other useful descriptors is poor on projection images through dense tissue.\(^21\)
Diagnostic tests are offered to people for whom there is suspicion of breast cancer, either due to their symptoms or screening test results. These tests are used to determine the presence and boundary of cancer, and to collect more information about the cancer for future treatment.1 Diagnostic tests assess the level of suspicion of malignancy of a lesion and a biopsy can be performed for the confirmation of cancer. The two main tests used for diagnosing breast abnormalities are mammograms and ultrasound with MRI less frequently used as a diagnostic tool.

Several studies22-26 have assessed the sensitivity and specificity of diagnostic mammography independently and reported various values. The variation in the sensitivity and specificity in these studies could have been caused by differences in the patient population, follow-up methods, the methods used to detect false negative cancers, and the amount of screening prior to the diagnostic mammography.26 Hence those results are not comparable26 and Moskowitz27 proposed that sensitivity and specificity of the diagnostic mammography might be expected to be 80-85% and 87%, respectively.

To aid with the communication of mammographic interpretation, the American College of Radiology (ACR) published the Breast Imaging Reporting and Database System (BI-RADS). This system demonstrates good correlation with the likelihood of breast malignancy and has improved patient care because it leads to proper follow-up test and procedures.28

Ultrasound has become a valuable diagnostic tool to use in conjunction with mammography because it is widely available and cost-effective especially when compared to MRI. The common use of ultrasound in breast imaging is to distinguish between cysts (fluid-
filled sacs) and solid masses. However ultrasound can sometimes help with differentiating benign from malignant solid masses. Ultrasound is most useful in assessing very dense breasts because, as mentioned previously, the sensitivity of mammography for the dense breasts is low, with values reported in the range of 35–48%.  

Diagnostic ultrasound has made considerable progress since the early 1990s in differentiating benign from malignant tumors. Several sonographic features such as margin, shape, and echo texture have been proposed for the assessment of breast masses. Malignant masses are often characterized by poorly defined margin, irregular borders, spiculation, microlobulations, hypo-echogenicity, shadowing, duct extension, and tissue architectural distortion. Benign masses, on the other hand, mostly have well-defined and circumscribed boundaries, round or oval shape with gentle bi- or tri-lobulations. Several studies evaluated the general applicability and inter-observer variability of sonographic features in differentiating benign from malignant solid breast masses. Arger et al. found that the interpretation of four different readers were comparable when standardized descriptors of breast masses were applied, and Rahbar et al. claimed that certain ultrasound features can help with differentiating benign from malignant masses but pointed out the need to investigate their practice and interpreter variability. In response to previous investigations, the ACR developed the first edition of a lexicon for breast ultrasound, the ultrasound breast imaging reporting and data system (US BI-RADS), to standardize the interpretation and reporting of breast masses in ultrasound. Hong et al. demonstrated that the US BI-RADS descriptors, margin, shape, orientation, lesion boundary, echo pattern, and posterior acoustic features can be used in differentiating benign from malignant masses, with positive predictive values (PPV) for malignancy of 62–86%. The PPVs reported by
Hong et al.\textsuperscript{41} were comparable to ones (68-81\%) of BI-RADS descriptors for mammography reported by Liberman et al.\textsuperscript{42}

The current clinical analysis of breast ultrasound images is mainly done qualitatively. Conventional B-mode imaging itself is a qualitative modality because image brightness and other features of displayed echo signals depend on operator settings and on system- and tissue-dependent factors. Thus most solid masses viewed on ultrasound require core biopsy to provide a definitive diagnosis, which results a high number of biopsy of benign tumors. The biopsy of benign masses cause unnecessary stress and cost to the patient and the healthcare system.\textsuperscript{37} The US BI-RADS lexicon has provided standardized breast imaging terminology, report organization, assessment structure, and tissue classification. It has helped to communicate, facilitate research, and provide better care for patients. However, most US BI-RADS descriptors are subjective and qualitative and inter-observer disagreement for some descriptors have been reported.\textsuperscript{43-45}

Computer-aided diagnosis (CAD) has been developed to aid in routine clinical evaluation of ultrasound breast images. This could improve the specificity of ultrasound breast imaging diagnosis, and interest in ultrasound CAD is growing.\textsuperscript{46} CAD systems use adaptive classifiers and learning algorithms to interpret various patterns shown in ultrasound images. CAD systems are increasingly being used for mammograms and their use in MRI has increased. Several studies on ultrasound CAD have demonstrated its benefits with ultrasound image interpretation.\textsuperscript{47-51}

Quantitative Ultrasound (QUS) is being studied as a means of aiding in the diagnosis of breast masses. QUS methods extract estimates of attenuation and backscatter on an absolute
scale as well as other features that depend directly on acoustic wave-tissue interactions in an
effort to characterize tissue and masses quantitatively and improve interpretation of conventional
ultrasound images. QUS has shown potential for detecting diffuse disease and for diagnosing
focal lesions. For example, measurements of ultrasound attenuation were used to differentiate
fatty liver from normal liver.\textsuperscript{52,53} Other researchers have demonstrated that ultrasound attenuation
has diagnostic value in trabecular bone,\textsuperscript{54} cortical bone,\textsuperscript{55} and in the breast.\textsuperscript{56,57} In addition
spectral analysis of backscattered echo signals has been used successfully to differentiate benign
from malignant masses in the eyes\textsuperscript{58} and in lymph nodes,\textsuperscript{59,60} and to outline high-risk regions to
guide prostate biopsies.\textsuperscript{61} A scatterer size estimator based on model fits to ultrasound echo signal
power spectrum data was successfully applied to backscatter data to accurately estimate
glomerular and arteriole sizes in kidneys.\textsuperscript{62} Also preliminary data have been obtained to evaluate
the role of QUS in areas such as identifying malignant thyroid nodules\textsuperscript{63} and liver masses.\textsuperscript{64}
Finally, estimation of the effective scatter diameter from backscattered echo signal power spectra
differentiated rat mammary fibroadenomas from 4T1 mouse carcinomas.\textsuperscript{65}

Our interests are in quantifying attenuation and backscatter properties in breast masses.
Some features of the US BI-RADS lexicons are used to describe echo patterns and posterior
acoustic features of breast masses, and these should correlate with QUS parameters. For example,
under US BI-RADS, the echo patterns of breast masses are categorized as anechoic, hyperechoic,
complex, hypoechoic, and isoechic. Similarly posterior acoustic features are described as none,
enhancement, shadowing, and combined. Although these descriptors are closely related to the
backscatter and the attenuation properties of breast masses, the evaluation of these features is
qualitative and subjective.
The purpose of this dissertation is to perform quantitative ultrasound imaging (QUS) of *in vivo* breast tumors in order to provide new tools to differentiate benign from malignant breast masses. We will test the following hypotheses: 1) quantified attenuation and backscatter will agree with the US BI-RADS interpretation of posterior echo features and echo pattern; 2) quantitative measures will remove the subjectivity in interpretation of attenuation and backscatter; and 3) this quantification will lead to better communication among health care providers. We also investigate attenuation, backscatter, and effective scatterer diameter (described in Chap. 2) as differential bio-markers for breast ultrasound diagnosis. Tissue-mimicking phantoms and animal breast tumor models were also studied for verifying and establishing the methods.

This dissertation is organized as follows:

In Chapter 2 the ultrasound attenuation coefficient, the backscatter coefficient, and the concept of “effective scatterer diameter” are introduced. Practical methods for measuring these quantities using clinical ultrasound instruments are presented. The acoustic scattering theories of Faran\(^66\) and Anderson\(^67\) are used to predict backscatter levels from phantoms, so they are briefly introduced. Finally, in vitro studies on acoustic properties of breast tissues are described.

In Chapter 3, estimated backscatter coefficients are presented for four homogeneous tissue-mimicking phantoms. These phantoms, described in detail in that chapter, have different scatterer size distributions and low attenuation properties and are used to test parameter estimation methods for known materials. Their backscattering properties are estimated using the
physical properties of materials used in their construction as input into the scattering theory of Faran or Anderson.

Chapter 4 presents attenuation and backscatter estimates in layered tissue-mimicking phantoms. One of the challenges for quantitative ultrasound in \textit{in vivo} application relates to the (often inhomogeneous) tissue paths between the ultrasound transducer and the region of interest (ROI). The layered phantoms were designed to mimic non-uniform tissue paths. The attenuation and backscatter in the layers were estimated and compared with theoretical values based on the phantoms’ constituent materials as well as laboratory measurements, made on test samples containing phantom component materials.

Chapter 5 presents attenuation, backscatter coefficients, and effective scatterer diameter estimates from experiments in animal models of breast tumors. Our estimates were compared with the results from two other research groups which used three different clinical imaging systems.

In Chapter 6, the reliability of the estimates presented in Chapter 5 is investigated using a phantom mimicking the animal tumor model. The experiments with the animal tumor model introduced challenging conditions such as lesion geometry and high attenuation in the tumor, and the phantom was designed to mimic those conditions. Backscatter and attenuation coefficients were estimated from the two tumor-mimicking lesions in the phantom using methods analogous to those presented in Chapter 5. These estimates were compared with the laboratory measurements and theoretical predictions.
Chapter 7 introduces a new method for estimating an effective attenuation coefficient from the transducer to a ROI and the ROI’s backscatter coefficient simultaneously. Backscatter and scatter diameter estimations are generally performed using spectral information derived from RF echo signals. However, the spectral information needs to be corrected for the frequency-dependent attenuation in the intervening tissue between the transducer surface and the ROI, and this method estimates the effective attenuation up to the ROI. The new method was tested on uniform and layered tissue-mimicking phantoms.

Chapter 8 presents preliminary estimates of attenuation coefficient, backscatter coefficient, and effective scatterer diameter for in vivo breast masses. The local attenuation values were estimated using the reference phantom method (RPM) and the hybrid method, both described in Chapter 2. Those values were correlated with the “posterior echo features” described by US BI-RADS descriptors. The backscatter coefficients were estimated after correcting echo signal power spectra for the attenuation along the tissue paths above the ROI using the effective attenuation coefficients obtained by the least squares method described in Chapter 7.

Chapter 9 presents a study on the effects on attenuation estimates using the reference phantom method when there is a mismatch in speed of sound between the reference phantoms and the test medium. An explicit assumption in the reference phantom method, needed to account for diffraction effects, is that the sound speeds in the two media match and that, in an array-based imaging system, that sound speed is used for time delays in beam formation and spatial registration. The effects of violating these assumptions are investigated in Chapter 9.
Guidelines for improving the accuracy of attenuation estimates in media with unknown sound speed are offered.

Finally, Chapter 10 discusses limitations of the current studies presented in this dissertation and suggests improvements and future work.

1.1 References


Chapter 2:
Attenuation and Backscatter Measurement
Methods and Previous Breast Studies

2.1 Attenuation Estimation

Attenuation in ultrasound means the amplitude reduction of the ultrasound wave as a function of frequency and distance as the wave propagates through the medium. Understanding attenuation effects is important because it provides useful diagnostic information and can lead to better interpretation of B-mode images. Additionally, in the case of quantitative ultrasound (QUS: parametric imaging) being developed at the University of Wisconsin Ultrasound Research Labs, attenuation plays a crucial role because parts of QUS strategies rely upon features of the echo signal power spectrum. The shape of the power spectrum is sensitive to the frequency-dependent attenuation, requiring attenuation corrections in order to derive meaningful “normalized” power spectrum estimates.

Measurement of ultrasound attenuation in soft tissue in vivo is challenging for several reasons. First, attenuation measurements are usually performed using backscattered echo signals originating from along the direction of an interrogating acoustic beam. Most backscattered signals from soft tissue arise from an ensemble of scatterers which are smaller than the wavelength of the ultrasound pulse. As a result the random nature of the echo signals limits the spectral estimation precision and spatial resolution obtainable in an attenuation estimate.
Another obstacle is the frequency dependence of attenuation, which is often assumed to be linear. However, the frequency dependence of attenuation may not be linear and could vary from one tissue to another. Thus, attenuation could distort the spectral characteristics of the interrogating pulses and echo signals in an unexpected fashion. Many factors such as the bandwidth of the incident pulse, the beam profile, the transmit pulse center frequency, the presence of specular reflectors, frequency-dependence of attenuation, and the scattering properties of the medium, have affected the development and use of attenuation measurement methods.

Attenuation measurement strategies have been studied by many researchers over several decades. These strategies can be classified as either time-domain or frequency-domain approaches. Moreover, there is a duality between both domains since characterizing a signal in one domain also provides its description in the other. In general, time-domain techniques are easier to implement and faster in computation time than are frequency-domain techniques. However, since time-domain techniques have difficulties in compensating for local variations (i.e., diffraction effects) in the ultrasound field along the beam propagation path, more frequency-domain techniques have been developed and investigated.

There are two fundamental approaches used to estimate attenuation in the frequency domain, namely the spectral difference method and the spectral shift method. Spectral difference methods track the reduction of the echo signal power spectra along the beam propagation path. These methods assume that the scattering properties (i.e., the backscatter coefficient) of the sample are unchanged over the depth range tracked. Echo signals from a
reference phantom whose acoustic properties are known are also obtained using the same equipment and system settings. Then the difference (or ratio) of power spectra from the sample and reference at two different depths yields the attenuation coefficient of the scanned object at the frequency and depth of interest. System effects such as diffraction, focusing, and time gain compensation, are accounted for by applying the reference phantom.

Spectral shift methods, on the other hand, utilize a downshift of the power spectra toward lower frequencies as the beam propagates in the attenuating medium. This shift in the power spectra obtained from two different depths is related to the attenuation characteristics of the object that is scanned.

Fink et al. developed a method using the spectral centroid from the power spectra obtained with short-time Fourier transform. They applied the non-invariant filtering to remove diffract effects from the power spectrum. Kuc et al. also suggested a centroid estimator using a second-order autoregressive model applying to the autocorrelation function of the echo signal. Baldeweck et al. proposed a second-order autoregressive model (AR2), whose parameters were estimated with the Burg algorithm, to estimate the center frequency of the echo signal over the depth. They compared the performance of the method with one of the classical short time Fourier analysis based on a Fast Fourier Transform. They found that their AR2 model provided a higher accuracy in attenuation estimates with the same precision level. The challenge with these autoregressive models is the selection of the order of autoregressive models, which is closely related to the accuracy and precision of attenuation estimates.
Generally, the attenuation estimation techniques using a spectral shift are more robust at the boundary region of backscatter changes than spectral difference methods while they are more sensitive to local spectral noises and have a difficulty of accounting for the imaging system-dependent factors including diffraction effects.\textsuperscript{12}

2.1.1. The reference phantom method

Several methods have been developed that utilize the spectral difference for attenuation estimations. Ophir \textit{et al.}\textsuperscript{13} utilized the difference in the spectra from two different depths using narrowband excitation pulses. A similar approach was suggested by Kuc\textsuperscript{14} in measuring the attenuation in liver tissue, although without bandwidth limitation. Wilson \textit{et al.}\textsuperscript{15} applied a least squares method to the power spectra to estimate the attenuation slope at each frequency and each depth. Yao \textit{et al.}\textsuperscript{7} developed the reference phantom method (RPM) which uses a reference phantom to account for the system-dependent factors, including diffraction. The RPM provides accurate results for attenuation estimations when data are acquired using clinical ultrasound systems if the speed of sound in the reference closely matches that of the sample. Since the RPM has an advantage of accounting for system dependent factors more easily and effectively than other spectral difference methods described above\textsuperscript{7}, the RPM was used most extensively in this dissertation. This section describes the method in more detail.

Assuming that soft tissue is weakly scattering so that multiple scattering can be ignored (first-order Born approximation), and that the distance from the transducer to the region of
interest (ROI) is greater than the transducer aperture, the power spectrum of the backscattered
RF echo signals from the region can be written as

\[ S(f, z) = G(f, z) \cdot D(f, z) \cdot A(f, z) \cdot B(f), \]  

(2-1)

where \( f \) denotes frequency and \( z \) represents the depth of the region of interest. \( S(f, z) \) is the
power spectrum of the backscattered echo signal and \( G(f, z) \) represents the combined
transducer electro-acoustic and acousto-electric effects from transmitting and receiving an RF
signal. \( G(f, z) \) depends on factors such as the transducer design, pulsing characteristics and
receiver gain. \( D(f, z) \) accounts for beam forming and diffraction effects, \( A(f, z) \) represents the
total attenuation over the path from the transducer surface to the depth of interest, and \( B(f) \) is
the backscatter coefficient (BSC) vs. frequency in the ROI.

Yao et al.\(^7\) have shown that for uniform samples, the ratio of the echo signal power
spectrum from a sample to that from a reference medium can be described as:

\[
\frac{S_{\text{sam}}(f, z)}{S_{\text{ref}}(f, z)} = \frac{G_{\text{sam}}(f, z) D_{\text{sam}}(f, z) B_{\text{sam}}(f) \exp(-4\alpha_{\text{sam}}(f)z)}{G_{\text{ref}}(f, z) D_{\text{ref}}(f, z) B_{\text{ref}}(f) \exp(-4\alpha_{\text{ref}}(f)z)}. \]  

(2-2)

The subscripts \( \text{sam} \) and \( \text{ref} \) denote the sample and reference medium respectively. The total
attenuation \( A(f, z) \) in Eq. (2-1) is modeled as \( \exp(-4\alpha(f)z) \), where \( \alpha(f) \) is the attenuation
coefficient in the medium. Power spectra are typically computed by averaging periodograms
within windowed regions of the RF echo signal whose axial extent are about 3-5mm. It is
assumed that any differences in attenuation between the sample and reference phantom over these short signal segments do not affect computations of acoustic properties.

There are three depth-dependent parameters in Eq. (2-1): \( G(f, z) \), \( D(f, z) \), and \( \exp(-4\alpha(f)z) \). The RPM makes two additional assumptions related to these parameters: (a) the sound speed within the reference medium is approximately the same as that of the sample, and (b) for array systems, the sound speed used in the system’s beamformer is the same as that of the sample and reference medium. Using these two assumptions, Eq. (2-2) can be simplified to

\[
\frac{S_{\text{sam}}(f, z)}{S_{\text{ref}}(f, z)} = \frac{B_{\text{sam}}(f)}{B_{\text{ref}}(f)} \exp(-4(\alpha_{\text{sam}}(f) - \alpha_{\text{ref}}(f))z). \tag{2-3}
\]

For an ROI with constant backscatter properties, the RPM estimates the attenuation of the sample using

\[
\alpha_{\text{sam}}(f) = -\frac{\ln \left( \frac{S_{\text{sam}}(f, z_2)}{S_{\text{ref}}(f, z_2)} \right)_{z_1} - \ln \left( \frac{S_{\text{sam}}(f, z_1)}{S_{\text{ref}}(f, z_1)} \right)_{z_2}}{4(z_2 - z_1)} + \alpha_{\text{ref}}(f), \tag{2-4}
\]

where \( z_1 \) and \( z_2 \) are depths in the ROI and \( z_2 > z_1 \).

2.1.2. Spectral Shift method

A classic analysis\(^{16} \) of the frequency shift method assumes the power spectrum of the backscattered ultrasound signal at depth \( z \) has a Gaussian shape given by:

\[
\]
\[ P(z, f) = S_0 \cdot \exp \left\{ -\frac{(f - f_z)^2}{2\sigma^2} \right\}, \quad (2-5) \]

where \( S_0 \) is a constant related to the initial transmit power and \( f \) represents the frequency. The shape parameters \( f_z \) and \( \sigma^2 \) represent the center frequency at depth \( z \) and the “variance” (i.e., the bandwidth) of the transmit pulse, respectively. Such a spectrum for the backscattered ultrasound signal can be closely approximated by a sinusoidal pulse modulated by a Gaussian envelope.\(^{16}\)

Under the assumption of linear frequency-dependent attenuation, the power spectra of backscattered signals at two depths, \( z_1 \) and \( z_2 \) (\( z_1 < z_2 \)), maintain the Gaussian shape, but with different center frequencies. The relationship between the two center frequencies at the different depths can be written as

\[ f_{z_2} = f_{z_1} - 2\sigma^2\beta(z_2 - z_1), \quad (2-6) \]

where \( f_{z_1} \) and \( f_{z_2} \) are the center frequencies at depth \( z_1 \) and \( z_2 \) respectively, and \( \beta \) represents the attenuation coefficient of the region between \( z_1 \) and \( z_2 \).\(^{16}\) Determining the value of \( \beta \) from the downshift in the center frequency of the backscattered signal spectra is referred to as the “classic frequency shift” method.\(^{8,16}\)

2.1.3. Hybrid method
The classic spectral shift method does not account for diffraction effects on the ultrasound signal. To address this limitation, a “hybrid method” has recently been introduced by our research group. This method was developed by combining the advantages of the classical frequency shift and spectral difference methods to overcome their specific limitations. Classical frequency shift approaches for estimating attenuation are more sensitive to local spectral noise artifacts and have difficulty in compensating for diffraction effects due to beam focusing. Spectral difference approaches, on the other hand, fail to estimate attenuation values accurately at tissue boundaries where the backscatter characteristics vary, thereby violating the assumptions used in this approach. In the hybrid method the echo signal power spectrum is divided by the power spectrum from a well-characterized reference phantom to reduce the impact of system-dependent parameters including diffraction effects. The power spectrum ratio, which might include backscatter variations, is filtered using a Gaussian function centered at the transmit center frequency of the imaging system. The spectral cross-correlation algorithm, is then used to compute spectral shifts from these filtered power spectra to estimate the attenuation coefficient. To summarize, the hybrid method utilizes the following equation to model the echo signal power spectrum as a function of depth:

\[
S(f,z) = P(f) \cdot D(f,z) \cdot A(f,z) \cdot B(f),
\]  

(2-7)

where \(S(f,z)\) is the power spectrum of the backscattered RF signal at depth \(z\). \(P(f)\) represents the combined effect of the transmit pulse and transducer sensitivity (electro-acoustic and acousto-electric transfer functions), which depends on the transducer design and the transmitted pulse.
\( D(f, z) \) denotes the effect of diffraction related to the geometry of the transducer, and \( A(f, z) \) represents the cumulative attenuation at depth \( z \). Assuming the attenuation has a linear-frequency dependence, the cumulative attenuation can be expressed as

\[
A(f, z) = \exp(-4\alpha f z),
\]

where \( \alpha \) is the slope of the attenuation coefficient versus frequency, in units of neper/cm-MHz.

\( B(f) \) describes the frequency dependence of the backscattered echo signals as a power-law function of frequency. This term may be expressed in a Taylor series expansion of its exponential form as follows:

\[
B(f) = f^n = \exp \left\{ n \cdot \log(f) \right\}
\]

\[
= \exp \left\{ n \cdot \log(f_c) + n \cdot \log \left(1 + \frac{f - f_c}{f_c}\right)\right\}
\]

\[
\approx f_c^n \cdot \exp \left\{ n \cdot \left( \frac{f - f_c}{f_c} - \frac{(f - f_c)^2}{2 f_c^2} \right) \right\}
\]

\[
\propto \exp \left\{- \frac{n \cdot (f^2 - 4 f_c f)}{2 f_c^2} \right\},
\]

where \( f_c \) is the center frequency of the pulse. To eliminate instrument and transducer-dependent terms, the ratio of the intensity of the backscattered RF signals from the sample to that from a reference phantom is used. This is written as:
\[
RS(f, z) = \frac{B_s(f)}{B_r(f)} \cdot \exp \left\{ -4 (\alpha_s - \alpha_r) f z \right\}
\]

\[
= \exp \left\{ -\frac{(n_s - n_r) \cdot (f^2 - 4 f_c f)}{2 f_c^2} \right\} \cdot \exp \left\{ -4 (\alpha_s - \alpha_r) f z \right\},
\]

(2-10)

where the subscripts \( r \) and \( s \) represent the reference phantom and sample, respectively. As mentioned previously, Kim and Varghese\textsuperscript{17} further apply a Gaussian filter to the ratio of the echo data. Then the Gaussian-filtered intensity ratio is given by

\[
GRS(f, z) = G(f) \cdot RS(f, z)
\]

\[
= \exp \left\{ -\frac{(f - f_c)^2}{2\sigma^2} \right\} \cdot \exp \left\{ -\frac{(n_s - n_r) \cdot (f^2 - 4 f_c f)}{2 f_c^2} \right\}
\]

\[
\cdot \exp \left\{ -4 (\alpha_s - \alpha_r) f z \right\},
\]

(2-11)

where \( G(f) \) is a Gaussian function centered at the transmit center frequency, \( f_c \), and has the same variance (bandwidth) as the original transmit pulse, \( \sigma^2 \). Finally, the center frequency of \( GRS(f, z) \) at depth \( z \) can be expressed as\textsuperscript{17}

\[
f_c(z) = \frac{f_c - 4\sigma^2 (\alpha_s - \alpha_r) z + \frac{\sigma^2 (n_s - n_r)}{f_c^2}}{1 + \frac{\sigma^2 (n_s - n_r)}{f_c^2}}
\]
\[
\alpha_s (dB/ cm - MHz) = -\frac{8.686}{4\sigma^2} \frac{df_c(z)}{dz} + \alpha_s,
\]

(2-13)

where \(z\) is the depth of the region of interest from the transducer and \(\sigma^2\) is the variance of the transmit pulse. The term \(f_c(z)\) denotes the center frequency of the GRS \((f, z)\) at depth \(z\).

### 2.2 Scattering theory

Phantoms used in this thesis work have either glass beads scatterers or agar sphere scatterers. For theoretical predictions of the backscatter coefficient in these materials, Faran’s scattering theory\(^\text{18}\) is applied for the glass beads spheres and Anderson’s theory\(^\text{19}\) is applied for phantoms with agar spheres.

Faran’s theory of the scattering of sound waves by an isotropic solid sphere and by cylindrical scatterers was introduced in 1951. The theory extended a previous study\(^\text{20}\) by taking into account shear waves as well as compressional waves. Burke \textit{et al.}\(^\text{21}\) demonstrated agreement between a measured scattering cross section vs. angle and Faran’s theory for a single steel sphere. Davros \textit{et al.}\(^\text{22}\) extended that work by demonstrating that ‘clouds of spherical scatterers’ could be modeled using Faran’s theory. Other studies\(^\text{23-27}\) used sphere scatterers having various diameter
ranges contained in a medium of agar or gelatin and showed that the measured backscatter coefficients agreed with Faran’s theory.

In our studies, the first twenty-five terms of the Faran model are used to calculate the predictions of the scattering cross section. Input to the model includes the sphere diameter distribution, the number of spheres per unit volume, Poisson’s ratio of the spheres, sound speeds of the spheres and the background material, and the mass density of the spheres and the background material.

Anderson’s scattering theory computes the scattered intensity from a fluid sphere in a fluid background; thus it does not consider shear waves. We apply Anderson’s theory to predict the scattering in phantoms with agar spheres, presented in Chap. 3. The first twenty-five terms of the Anderson’s solution are used to calculate the predictions of the scattered intensity. The density and compressional wave sound speed of the fluid spheres and of the background material are utilized in the calculation.

2.3 Estimation of the Backscatter Coefficient (BSC)

The BSC is defined as the differential scattering cross section per unit volume for a scattering angle of 180°. BSCs can be estimated as a function of frequency using the reference phantom technique applied to the RF echoes. Using Eq. (2-3) in 2.2.2, the BSC of a sample is estimated by

\[
B_{sam}(f) = \frac{S_{sam}(f, z) \exp(4 \alpha_{sam}(f)z)}{S_{ref}(f, z) \exp(4 \alpha_{ref}(f)z)} B_{ref}(f),
\]

(2-14)
where $S(f, z)$ is the value of the power spectrum of the backscattered RF signal at frequency $f$ and depth $z$, $B(f)$ is a BSC function of frequency, $\exp(-4\alpha(f)z)$ is the total attenuation at depth $z$, and $\alpha(f)$ is the attenuation coefficient in the medium. The subscripts $sam$ and $ref$ denote the sample and reference medium, respectively.

The BSC function is estimated by multiplying the ratio of the attenuation-corrected power spectrum from the sample to that of the reference, with the BSC function of the reference. Since the power spectrum is calculated using a gating window of finite length, the proper attenuation correction scheme is necessary, especially when a medium has a large attenuation coefficient and a long gating window is used. Oelze and O’Brien\textsuperscript{28} investigated the effects of using different attenuation-compensation functions to account for losses in the normalized power spectrum. They compared three attenuation correction methods, namely point compensation\textsuperscript{29,30}, O’Donnell and Miller compensation\textsuperscript{31}, and Oelze and O’Brien compensation.\textsuperscript{28} This group estimated and compared the average scatterer diameter from the normalized power spectrum when compensated by each of the methods. While O’Donnell and Miller compensation and Oelze and O’Brien compensation produced smaller errors with a long gating window, the performance of the three methods was comparable with a window length of 0.5-5mm. The window length used in the studies presented in this dissertation was 3-5mm, and the point compensation method was applied to correct for attenuation in estimating backscatter coefficients and effective scatterer diameters. The point compensation method sets $z$ in Eq. (2-14) as $z_0 + L/2$, where $z_0$ is the distance between the transducer and the edge of gated region and $L$ is the gating window length.
2.4 Effective Scatterer Diameter Estimation

Conventional B-mode imaging uses the envelope of RF ultrasound signals to modulate the intensity of display. Thus, B-mode imaging ignores any frequency-dependent information in the echo signal. However, the frequency dependence of the backscattered signal can provide additional information related to the microstructure of tissue. The effective scatterer diameter (ESD) and, potentially, the acoustic concentration (product of the number concentration of scatterers and the relative impedance difference between the scatterers and surrounding tissues) are useful descriptors of the tissue microstructure and therefore might aid in diagnosing disease and estimating the stage of disease.

Soft tissues may be modeled as fluids containing either discrete or continuous inhomogeneities with varying intensity and compressibility. The structure or morphology of tissue is assumed to consist of small, randomly positioned inhomogeneities and the statistical properties of the random medium are assumed to be stationary in time and homogeneous in space. Since most analyses of this type are limited to first- and second-order statistical properties, the condition that the medium is weakly stationary is sufficient. In fact, time varying factors, such as scattering from flowing blood, are negligible as compared to scattering from tissue parenchyma, and thus the assumption of a weakly stationary process generally is reasonable.

We assume that the speed of sound is constant over the range of frequencies analyzed since dispersion is known to be small in biological material. However, ultrasound waves traveling through tissue undergo attenuation losses, which needs to be corrected before
estimating a backscatter coefficient of an effective scatterer diameter. This makes the measurement of attenuation an important process.

Estimation of the ESD uses the frequency dependence of the backscatter coefficient. Fundamentally, the ESD can be directly related to the correlation length of inhomogeneities in the medium.\textsuperscript{28} Based on the established framework of single-scattering theory,\textsuperscript{38} the backscatter coefficient and the correlation function for the medium are connected through an acoustic form factor. An intensity form factor $F$ is defined\textsuperscript{29} as the ratio of the backscatter coefficient for a test material having scatterers with finite size to that of a similar material consisting of Rayleigh ("point") scatterers:

$$F(2k) = \frac{\sigma_b}{\sigma_0},$$

(2-15)

where $k$ is the wave number, $\sigma_b$ is the backscatter coefficient of the test material, and $\sigma_0$ is the backscatter coefficient of a similar material consisting of point scatterers. The acoustic form factor is related to the spatial Fourier transform of the correlation function for the medium, and explains the spatial distribution and organization of the scatters in the frequency domain.\textsuperscript{29} The common form factor models are the fluid sphere, spherical shell, and Gaussian models. Depending on the test material, the proper form factor is chosen by empirical knowledge of the scattering medium and compared with the form factors which are calculated for a range of particle sizes. The ESD is determined by looking for the corresponding backscatter model that
yields the minimum average squared deviation between the theoretical and measured form factors for that diameter.\textsuperscript{29} Some measure of the ‘quality’ of the fit, such as a Chi-squared statistic\textsuperscript{30} is used to determine whether the model adequately fits the data.

The current form factor models, including the fluid sphere model, the spherical shell model, and the Gaussian form factor have some limitations. They cannot be utilized reasonably when $ka$ ($k$: wave number, $a$: scatterer radius) is much greater than one or if shear waves are involved with scattering.\textsuperscript{29}

Later in this dissertation, ESDs are computed for animal tumor models and \textit{in vivo} breast masses. The ESDs are estimated from the BSCs using a Gaussian form factor, a model used by many researchers for describing scattering from biological tissues.\textsuperscript{33,39-41} The advantage of a Gaussian model is that there is a closed solution derived by Gerig \textit{et al.}\textsuperscript{42} as presented here.

The scattering sources are assumed to be continuously varying fluctuations in the acoustic properties of the medium and their spatial correlation can be described with Gaussian random variable\textsuperscript{29}. The BSC function can be expressed in terms of that correlation function as\textsuperscript{42}:

$$BSC(k) = C k^4 \int_{-\infty}^{\infty} b_\gamma(\Delta r) e^{-i2k\cdot\Delta r} d\Delta r,$$

which is valid for sparse media when scattering is weak, and shear wave effects are negligible. $C$ is a function of tissue properties and is independent of frequency. $k$ is the scattering vector, whose magnitude is $k$ (the wave number). $k$ points in the direction of insonification. $b_\gamma(\Delta r)$ is the correlation function of the medium, which is assumed to be statistically stationary. It is defined as:
\[ E \{ \gamma(r+\Delta r), \gamma(r) \} = E \{ \gamma^2(r) \} b_j(\Delta r), \]  

(2-17)  

where \( E \{ \} \) is expectation operator. \( \gamma(r) \) is the reflectivity of the medium at \( r \), and is a function of the fluctuation in acoustic properties at that location in the medium, \( \gamma(r) = (\kappa(r)-\kappa_0)/\kappa_0 - (\rho(r)-\rho_0)/\rho(r) \). \( \kappa \) and \( \rho \) are compressibility and density, respectively, and \( \kappa_0 \) and \( \rho_0 \) are their corresponding mean values.\(^{29}\) The correlation function for a Gaussian model is:

\[ b_j(\Delta r) = e^{-\Delta r^2/d}, \]  

(2-18)  

where \( d \) is a characteristic dimension \(^{35}\) and the relationship between the effective scatterer radius and \( d \) is\(^{42}\):

\[ 2a = (12\sqrt{2\pi})^{1/3}d \approx 3.1d = d, \]  

(2-19)  

Then the BSC is given by\(^{42}\):

\[ BSC(k) = C'k^4 e^{-2k^2d^2}, \]  

(2-20)  

where the ESD can estimated from the frequency dependence of the BSC. Generally, the ESD is determined by comparing the frequency dependence of the estimated BSC with that of the expected BSC, which can be pre-computed with a range of various scatterer sizes. In the case of a Gaussian model, the ESD can be estimated by a minimax approach\(^{45}\) and is given as:
\[ \hat{\sigma}^2 = \frac{-d_1^2 c^2}{80} \sum_{\omega_{\text{min}}}^{\omega_{\text{max}}} \left( y(\omega) \omega^2 - \bar{y} \omega^2 \right) \sum_{\omega_{\text{min}}}^{\omega_{\text{max}}} \left( \omega^2 - \bar{\omega}^2 \right)^2, \] (2-21)

where \( y(\omega) = 10 \ln(\text{BSC}(\omega)/\omega^4) \), \( c \) is the speed of sound, and \( d_1 \) is from Eq. (2-19).

Gerig \textit{et al.}\(^{42}\) investigated the variance of the ESD estimates from Eq. (2-21) and found that it directly increased by the square of the BSC values and decreased by increasing the bandwidth and the number of sample and reference power spectra. They also suggested the use of the angular compounding to reduce the variance of the ESD estimates by increasing the number independent of power spectra computed from a given location.\(^{44,45}\)

### 2.5 Speed of Sound in soft tissues

Measurements of the speed of sound in soft tissues have been important tasks for many researchers.\(^{46-48}\) Use of accurate speed of sound values in ultrasound imaging gives better B-mode image quality because the time delay settings of beamformers in an ultrasound scanner, which is related to transmit focusing and dynamic receive focusing, is based on the speed of sound. A failure to match sound speeds in the beamformer with those of the tissue causes a blurring of gray-scale images. Anderson \textit{et al.}\(^{49}\) reported quantitative results on the effects of sound speed errors in medical ultrasound imaging. The impact of a mismatch of the speed of sound in reference and sample media when making attenuation measurements has not been determined, however. Interestingly, the simulation results from the study by Chen \textit{et al.}\(^{50}\) suggest
that even small sound speed difference, such as 5-10 m/s, may cause artifacts in attenuation coefficient images.

Except for location where through transmission, reconstruction tomography can be applied, measuring the speed of sound in soft tissues *in vivo* is not simple. The speed of sound in tissues generally depends on the amount of fat, water, muscle, and connective tissues in the beam path. Reconstruction tomography$^{51}$ has been used for imaging tissue speeds of sound, but pulse-echo methods, which could be implemented during regular imaging procedures, are less well developed.

### 2.6 Breast Tumor Studies

Breast tumors can be categorized as either benign or malignant. Examples of non-cancerous (benign) tumors are fibroadenomas, simple cysts, ductal/lactating/tubular adenoma, and apocrine/ sclerosing/blunt duct/ micro-glandular adenosis.$^{52}$ Examples of cancerous (malignant) tumors are invasive/infiltrating ductal carcinoma, lobular carcinoma.

There have been several laboratory-based studies to quantify excised breast tissue properties. Landini *et al.*$^{53}$ studied BSCs from five groups of normal and pathological breast specimens as a function of frequency, at a single frequency, and as a function of the angle of incidence between the ultrasound beam and the specimen. Their results suggested that backscatter could be a potential classifier between normal and pathological tissues.

Motensen *et al.*$^{54}$ characterized normal, benign, and malignant breast tissue specimens by measuring the speed of sound, attenuation, and BSCs at 37°C. The study showed high accuracy
in classifying the tissues when the results were corrected for the within-patient mean; however, the data not corrected for the within-patient mean could not classify them correctly.

D’Astous and Foster\textsuperscript{55} measured the frequency-dependent attenuation and BSCs from excised breast tissue over the bandwidth of 3-7MHz. They found that attenuation in infiltrating carcinoma was higher than that in fat, but less than that in fibrous and parenchymal tissues. In addition they found that the BSC from ductal carcinoma was comparable to that of fat, but it was significantly lower than that of parenchymal tissue. Golub et al.\textsuperscript{56} presented preliminary results for differentiating breast tumors by calculating the slope and $Y$ intercept from the logarithmic form of the normalized power spectra. Finally, Oelze and O’Brien showed the feasibility of differentiating between benign and malignant breast tumors based on the ESD estimated from the ultrasound RF signal in mouse and rat models.\textsuperscript{57}

### 2.7 References


Chapter 3: Backscatter measurements in tissue mimicking phantoms

3.1 Introduction

We are developing and validating quantitative ultrasound (QUS) imaging methods that derive absolute attenuation and backscatter coefficients (BSCs) from tissues. The methods are based on analysis of radio frequency (RF) echo signals from the region of interest (ROI) and use scans of reference reflectors or reference media to account for system-dependent factors listed above.

The ultrasound BSC and its dependence on ultrasound frequency are fundamental to many types of QUS imaging. It is important, therefore, to demonstrate system and operator independence of BSC estimates for effective widespread use of these measurements. To this end several interlaboratory studies have been conducted using different experimental apparatus to estimate BSCs.\textsuperscript{1,2,3} These studies have enabled researchers to uncover sources of errors in measurements that, once eliminated, resulted in interlaboratory agreement among BSC estimates on identical samples.\textsuperscript{2,3}
The studies by Wear et al., Anderson et al., and King et al. focused on laboratory-based apparatus, measurement and data processing techniques. However, to apply QUS in a clinical setting, it is necessary to also demonstrate system and operator independence of BSC estimates using array-based ultrasound imaging systems. These systems generally exhibit greater variability in transducer geometry and beamforming functions than simple single-element transducer systems, and this makes calculation of pulse-echo beam properties as used for BSC data reduction more challenging. In addition, normalizing data using echo signals from planar reflectors, as performed in the above studies, is complicated in clinical machines because of dynamic focusing of the received beam, the high system sensitivity and use of internal TGC.

The goal of this study was to evaluate the accuracy of BSC estimates from a clinical ultrasound system equipped with a research interface using the reference phantom technique. RF echo data were acquired from well-characterized samples, used previously to verify performance accuracy of laboratory systems. BSC estimates from RF echo data acquired by a clinical imaging system were compared with the laboratory measurements as well as a theoretical model.

### 3.2 Method and Materials

#### 3.2.1. Tissue-mimicking phantoms

Four different tissue-mimicking phantoms were utilized in this study. The first tissue-mimicking phantom (Glass beads phantom) consists of 41 μm-diameter glass spheres in an agar gel background. The spheres have a narrow distribution of diameters (41±2μm). The other three samples contain weakly scattering agar spheres of various diameters in the background of
agarose and deionized water mixture. The detailed compositions of three weakly scattering samples are presented by King et al.\textsuperscript{3} The nominal size distributions of three agar spheres samples were 90-125µm (Agar-90 phantom), 125-150µm (Agar-125 phantom), and 180-212µm (Agar-180 phantom), respectively. The samples were 5-7.5cm-diameter, 2-3cm-thick cylinders with two circular transmission windows made of 25µm-thick Saran film\textsuperscript{®} (Dow Chemical, Midland, MI, USA). The photo of three Agar phantoms is shown in Fig. 3.1. The Glass beads phantom has the same appearance of them but was 7.5cm-diameter and 2.5cm-thick. The construction process of the sample was described by Madsen et al.\textsuperscript{4} and King et al.\textsuperscript{3}

\textbf{Figure 3.1.} Tissue mimicking samples; Agar sphere 90-125µm, Agar sphere 125-150µm, Agar sphere 180-212µm
The sample properties are presented in Table 3.1. Sound speed and attenuation coefficients were estimated\(^1\) using a narrow-band through-transmission technique\(^5\) with unfocused single element transducers at 22°C. The backscatter coefficients were measured using a broadband reference reflector method\(^6\) with focused single element transducers. A broadband reference reflector method determines the echo signal power spectrum within the sample, using the spectrum from a smooth planar interface, and modeling the 3-dimensional beam profile as well as the transmission and reception properties of the transducer-pulser-receiver used in the experiment. The unfocused and focused single-element transducers used for this study spanned 3.5-10MHz and 2.25-10MHz, respectively.

The attenuation loss per unit distance from each frequency was fit to a power law function of frequency. Fit parameters are also presented in Table 3.1. The backscatter measurements by the broadband reference reflector method are presented and compared with the BSC estimates from a clinical imaging system as well as theoretical predictions in Results and Discussion.

\(^1\) The attenuation estimation was done with low power level and minimum distance between the sample and transducer to prevent any possible non-linear propagation.
### Table 3.1. Composition and properties of the tissue-mimicking samples used for imaging system BSC estimates.

<table>
<thead>
<tr>
<th></th>
<th>Glass beads</th>
<th>Agar-90</th>
<th>Agar-125</th>
<th>Agar-180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number density (scatterers/mm³)</td>
<td>26</td>
<td>3.6</td>
<td>2.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Bead type</td>
<td>Borosilicate</td>
<td>agar</td>
<td>agar</td>
<td>agar</td>
</tr>
<tr>
<td>Sphere diameter (µm)</td>
<td>39-43</td>
<td>90-125</td>
<td>125-180</td>
<td>180-212</td>
</tr>
<tr>
<td>Sound speed of sphere</td>
<td>5572m/s</td>
<td>1492m/s</td>
<td>1492m/s</td>
<td>1492m/s</td>
</tr>
<tr>
<td>Poisson ratio of sphere</td>
<td>0.210</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Mass density of sphere</td>
<td>2.38g/cm³</td>
<td>1.03g/cm³</td>
<td>1.03g/cm³</td>
<td>1.03g/cm³</td>
</tr>
<tr>
<td>Background material</td>
<td>2% agar in water, n-propanol</td>
<td>2% agarose in water</td>
<td>2% agarose in water</td>
<td>2% agarose in water</td>
</tr>
<tr>
<td>Phantom density (g/cc)</td>
<td>1.00</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td>Sound speed (m/s)</td>
<td>1539</td>
<td>1491</td>
<td>1491</td>
<td>1491</td>
</tr>
<tr>
<td>Attenuation (dB/cm, f is frequency in MHz)</td>
<td>$0.027 f^{789}$</td>
<td>$0.03 f^{485}$</td>
<td>$0.03 f^{428}$</td>
<td>$0.03 f^{559}$</td>
</tr>
</tbody>
</table>

#### 3.2.2. Reference Phantom

To account for imaging system dependent effects on the RF echoes, a reference phantom technique was employed. (see Section 2.1.1) The reference phantom was made with 6.4g of 5-43µm-diameter glass beads evenly distributed in a 1600cc gel background. The background material was a gelatin emulsion containing 70% safflower oil. The top of the reference phantom was covered with a 25µm-thick Saran film®. The acoustic properties of the reference phantom were estimated using single-element transducers and a narrow-band substitution method on test
samples manufactured at the same time as the reference phantom. The sound speed was 1492m/s at 2.5MHz. Measured attenuation coefficients at frequencies from 2-10MHz were fit to a power law function of frequency, yielding \( \alpha(f) \ (dB/cm) = 0.256 f^{1.366} \), where \( f \) is the frequency in MHz.

### 3.2.3. Data collection and Analysis

A Siemens Acuson S2000 (Siemens Medical Solutions USA Inc., Malvern, PA), providing RF echo data through the manufacturer’s Axius Direct ultrasound research interface (URI)\(^9\), was used to image the four tissue-mimicking samples. A Siemens Acuson S2000 system is an array transducer system supporting linear, curvilinear, and phased arrays. The array transducer which is used as a transmitter and receiver has many elements (typically 64-256).\(^9\) This system has an electronic beamformer that controls transmit focusing and dynamic receiving focusing. The echo signals detected at the transducer’s receive mode impinge on the individual elements. Each echo signal collected from the transducer elements are combined by a beamformer forming a single acoustic beamline. The beamlines are stored with 16-bit resolution and 40MHz sample frequency. The URI provides theses minimally processed beamlines referring as “RF echo data.” A set of beamlines (typically 256-456 beamlines) comprise a “frame” of RF echo data. The RF echo is only processed by anti-alias filtering, beamforming, and the time gain compensation (TGC) gain whose information is stored in the file header.\(^9\) The RF data are read using Matlab\(^\circ\) (The MathWorks, Inc., Natick, MA) for offline analysis which including the attenuation and BSC estimation using the power spectra from segments of the data.

The glass beads sample was scanned using a 18L6 linear array transducer, using a nominal excitation frequency of 10MHz. The three agar spheres samples were scanned twice
using the same transducer, driven at a nominal excitation frequency of 6MHz or 9MHz. Five to ten frames of RF echo data were acquired with an elevational translation or rotation of the transducer between each frame to obtain statistically independent echo signals. The glass beads sample was scanned under water to reduce reverberations. The other data were acquired with the array transducer placed in contact with the sample. RF echo data were also obtained from the reference phantom described above, using the same transducer, transmit focus, and other equipment settings employed for the sample.

BSCs were estimated as a function of frequency using the reference phantom technique as described. The power spectrum was calculated by applying a Hann time-gating window to the RF data, computing the squared magnitude of the Fourier transform, and averaging over adjacent acoustic beamlines within a frame. The power spectrum analysis window size was 3mm (axially, 8 pulse lengths) by 3mm (laterally, 6 uncorrelated acoustic beamlines), and the overlap ratio was 75% both axially and laterally.

The ratio of the echo’s power spectrum from the sample to that from the reference phantom was obtained at each depth. The power spectra were then corrected for the difference between the attenuation losses for the sample path and the reference phantom path at each depth. Using the known BSC of the reference phantom, the BSCs of the tissue-mimicking phantom were estimated using Eq. (2-14) in Chapter 2. The BSCs obtained from each analysis window over the ROI were spatially averaged and presented as a function of frequency.

3.3 Results and Discussion
The estimated BSCs from all four tissue mimicking samples are displayed in Fig. 3.2. Also shown on Fig. 3.2 (a) is the BSC prediction using Faran’s theory\textsuperscript{10} for the glass beads phantom. Input parameters for the theoretical calculations include the mass density and sound speed of the background material, the mass density, sound speed, and Poisson’s ratio for the sphere scatterers as well as their diameter distribution and concentration (number of scatterers per unit volume). The input values used for the glass beads sample are presented in Table 3.1. For the agar spheres samples, the Anderson\textsuperscript{11} theory was used as theoretical prediction. The Anderson model assumes fluid scatterers in a fluid background and detailed calculation procedures for agar spheres samples are presented by King \textit{et al.}\textsuperscript{3} The input parameters for the agar sphere samples are also presented in Table 3.1.

From Fig. 3.2 (a), it can be observed that BSC estimates made with a clinical imaging system are in good agreement with values from Faran’s theory as well as the laboratory measurements. Possible causes of the discrepancy between the system estimates and theoretical values are factors such as minor localized differences in number density, and a small difference between the speed of sound in the reference and the sample, which was ignored. Nam \textit{et al.} have shown that errors in reference phantom-based attenuation estimates can occur even with small (2\%) differences in sound speed from sample to reference, depending on the focusing characteristics\textsuperscript{12}(see Chapter 9).
Figure 3.2. BSC estimates of tissue mimicking phantoms; (a) Glass beads, (b) Agar-90, (c) Agar-125, (d) Agar-180

From Fig. 3.2, it can be seen that BSC estimates from the clinical imaging system for the agar sphere samples are under-estimated. The laboratory BSC measurements also showed slightly lower magnitude than theoretical predictions except for the Agar-125 sample (Fig.3.2(c)). Possible cause of the magnitude discrepancy is the low signal to noise ratio (SNR) for the RF
echo data from the agar spheres samples. Note that the BSC of these samples are very low magnitude (very weakly scattering materials). Measuring BSCs from a weakly scattering material such as the agar phantoms studied here using a clinical scanner is much more challenging than using laboratory equipment because the laboratory equipment can time-average echo signals to improve the electronic signal-to-noise ratio of an echo signal, but an imaging system normally cannot. The short axial distance from the transducer to the ROI (axial distance varied from 2-3cm.) also could have led to reverberations in the ROI. A clinical scanner transmits pulses and receives echoes sequentially with a high pulse repetition frequency, which can cause reverberation artifacts by taking the bouncing echo from the preceding pulse as the echo from the current pulse.

However, the frequency dependence of BSC estimates from both of clinical scanner and laboratory agreed well with that of theoretical values. This is valuable since the effective scatter size estimation process depends more on the frequency dependence than the magnitude of BSC. Generally the BSC measurements using a clinical scanner are not easy compared to those with well-controlled laboratory setting. Each beamline is from the combined echo signals from many array elements of a transducer which are acquired under TGC, transmit focusing, and dynamic receiving focusing. Moreover, the agar phantoms are very weakly scattering and have short-axial length. Considering those difficulties, the BSC results shown in Fig. 3.2 are very encouraging.

3.4 Conclusion

BSC estimation of a glass bead tissue-mimicking sample using an ultrasound imaging system is consistent with predictions from Faran’s scattering theory in frequency dependence and
scattering magnitude. BSC estimates from three agar spheres samples showed good agreements with predictions in terms of the frequency dependence of the BSC while the magnitudes were lower than the theoretical values. These experimental results demonstrate that the BSC can be estimated accurately using a clinical imaging system and reference phantom data analysis techniques though the BSC estimation from very weakly scattering material can be more challenging. The findings illustrate the high potential to translate QUS imaging from the laboratory to clinical settings.

3.5 References


Chapter 4:
Attenuation and Backscatter estimates in layered tissue-mimicking phantoms

Portions of this chapter are being published as:

4.1 Introduction

One of the challenges for quantitative ultrasound (QUS) in vivo is correcting for inhomogeneous tissue paths between the ultrasound transducer and the ROI. Attenuation and viscous losses compete with scattering to affect the detected echo signals, and spatial variations in both properties along the propagation path complicate the estimation of the attenuation and backscatter coefficients for any ROI distal to such inhomogeneous layers. The goal of the work presented in this chapter is to assess the accuracy of backscatter and attenuation estimates from ROIs within layered phantoms that represent simple, but important first approximations to the inhomogeneous tissue propagation path in vivo.

4.2 Methods and Materials

4.2.1. Tissue mimicking layered phantoms

Three tissue-mimicking phantoms having spatial variations in backscatter and attenuation were constructed. Two “variable backscatter coefficient (VBSC)” phantoms were designed to have a uniform attenuation coefficient in all layers but the middle layer has 6dB higher
backscatter. The difference between the two VBSC phantoms is in the scatterer size distribution. One VBSC phantom (VBSC-24µm) includes 5-43µm glass spheres, with a median size of 24µm. The other VBSC (VBSC-49µm) phantom has 45-53µm diameter glass spheres, with a median diameter of 49µm. The “Variable attenuation (VA)” phantom was designed to have three layers with equivalent backscatter properties, but with the middle layer having a higher attenuation coefficient than the other two layers. Further details of the acoustic properties of these phantoms are presented in Fig. 4.1 and B-mode images acquired from the 18L6 transducer are presented in Fig. 4.2.

All three phantoms consist of water based gel with evaporated milk to control attenuation and microsphere glass spheres to provide scattering. Material concentrations and glass bead diameters are presented in Table 4.1. The layered surfaces are bonded together, and because the media are nearly identical in terms of their densities and sound speeds, reflection losses at the interfaces are negligible. The top layer, middle layer, and the bottom layer of the phantoms in the order as shown in Fig. 4.1 are defined as “layer 1”, “layer 2”, and “layer 3”, respectively. The phantoms are shaped as 9cm (laterally) x 9cm (elevationally) x 7cm (axially) cubes and sit in plastic storage containers filled with oil.

Speeds of sound, attenuation coefficients, and backscatter coefficients (BSCs) of the phantom layers were measured using 2.5cm-thick, 7.5cm-diameter cylindrical test samples manufactured during construction of the phantoms. Test samples have two parallel transmission windows of 25µm-thick Saran Wrap® (Dow Chemical, Midland, MI, USA). A narrow band substitution technique with matching pairs of unfocused transducers was applied to measure
attenuation coefficients over the 3.5-10MHz frequency range and speeds of sound at 3.5MHz. (A single frequency is sufficient as dispersion is negligible in these materials.) Sound speed of all sections of the phantoms were within the range of 1550±5m/s, except for layer 2 of the VA phantom, for which the sound speed was 1564m/s. Attenuation coefficients were fit to linear functions of frequency, and the slopes of the attenuation coefficient vs. frequency (dB/cm-MHz) were obtained over 3.5-10MHz. The attenuation measurement results for each section of the phantoms are presented in Fig. 4.1.

A broadband reference reflector method\(^3\) was applied to measure BSCs using focused single element transducers. The transducers spanned the 2.5-13MHz frequency range. The method consists of determining the echo signal power spectrum from the sample, applying the power spectrum from the reference reflector to account for the transducer’s pulse-echo sensitivity characteristics, and modeling the attenuated transducer field as well as effects of electronic gating on the echo signal. The BSC results obtained using the broadband reference reflector method are presented in the Results section along with results from clinical systems and theoretical predictions.
Figure 4.1. Description of VBSC-24µm, VBSC-49µm, and VA phantoms (BSC at 7MHz from Faran theory (see Section 2.2) is presented here): VBSC-24µm: nearly the same attenuation coefficient throughout, but a higher BSC in the middle layer with a median scatterer size of 24µm, VBSC-49µm: nearly the same attenuation coefficient throughout, but a higher BSC in the middle layer with a median scatterer size of 49µm, VA: the same BSC throughout, but with higher attenuation in the middle layer

<table>
<thead>
<tr>
<th></th>
<th>VBSC-24µm</th>
<th>VBSC-49µm</th>
<th>VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>α (dB/cm MHz)</td>
<td>BSC (cm⁻¹ar⁻¹)</td>
<td>α (dB/cm MHz)</td>
<td>BSC (cm⁻¹ar⁻¹)</td>
</tr>
<tr>
<td></td>
<td>0.52</td>
<td>0.91e⁻³</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>0.54</td>
<td>3.65e⁻³</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>0.52</td>
<td>0.91e⁻³</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Figure 4.2. B-mode images (with a18L6 transducer): (a) VBSC-24µm phantom, (b) VBSC-49µm phantom, (c) VA phantom
Table 4.1. Composition of layered phantoms: (a) VBSC-24µm, (b) VBSC-49µm, (c) VA

(a)

<table>
<thead>
<tr>
<th>Layer 1</th>
<th>Layer 2</th>
<th>Layer 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scatterer diameter</td>
<td>5-43µm</td>
<td>5-43µm</td>
</tr>
<tr>
<td>Number density</td>
<td>2g/l</td>
<td>8g/l</td>
</tr>
<tr>
<td>Background material</td>
<td>3:1 gel to milk</td>
<td>3:1 gel to milk</td>
</tr>
</tbody>
</table>

(b)

<table>
<thead>
<tr>
<th>Layer 1</th>
<th>Layer 2</th>
<th>Layer 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scatterer diameter</td>
<td>45-53µm</td>
<td>45-53µm</td>
</tr>
<tr>
<td>Number density</td>
<td>2g/l</td>
<td>8g/l</td>
</tr>
<tr>
<td>Background material</td>
<td>3:1 gel to milk</td>
<td>3:1 gel to milk</td>
</tr>
</tbody>
</table>

(c)

<table>
<thead>
<tr>
<th>Layer 1</th>
<th>Layer 2</th>
<th>Layer 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scatterer diameter</td>
<td>5-43µm</td>
<td>5-43µm</td>
</tr>
<tr>
<td>Number density</td>
<td>4g/l</td>
<td>4g/l</td>
</tr>
<tr>
<td>Background material</td>
<td>3:1 gel to milk</td>
<td>3:1 gel to milk</td>
</tr>
</tbody>
</table>

4.2.2. Reference phantom

As described in Chapter 2, attenuation and backscatter coefficients of an object can be estimated from the RF echo signals obtained from regions within the medium using a clinical scanner, but to do that, imaging system dependent factors that affect the echo signals need to be
accounted for. To do this for imaging system dependent factors on the RF echo data, a reference phantom technique was employed.\textsuperscript{4} In this study, layer 1 of the “VA phantom” was used as a reference after rotating it 90° to gain access to this uniform volume.

### 4.2.3. Data collection

A Siemens Acuson S2000 (Siemens Medical Solutions USA Inc., Malvern, PA) was used to image the tissue-mimicking layered phantoms. The instrument has been described in detail in Section 3.2.3. An 18L6 linear array and a 9L4 linear array transducer were utilized, with nominal excitation frequencies of 10MHz and 9MHz, respectively. Beamformed acoustic scan line signals were acquired through the Axius Direct research interface\textsuperscript{5} on the scanner.

The three layered phantoms and a reference phantom were scanned with the array transducer placed in contact with the phantom surface. Five separate frames of RF echo data, each consisting of 368 or 456 acoustic beamlines, were acquired with an elevational translation or rotation of the transducer between each frame to obtain statistically independent echoes. Prior to RF data acquisition, the scanner system settings, including time-gain compensation (TGC), overall gain, transmit focus position, and transmit power level were established for each phantom scan by adjusting controls until a uniform gray level over the entire depth of the phantom image was observed on the scanner’s B-mode image display. The same settings were then used for the scan of the reference phantom.

### 4.2.4. Attenuation estimation

Off-line analysis of the RF acoustic beamline signals was done using routines developed in Matlab\textregistered. This consisted of computing the echo signal power spectra over windows from
gradually increasing depths into the sample and dividing the power spectra by the spectra from the same depth in the reference phantom. The slopes of attenuation coefficient vs. frequency for the three layered phantoms were estimated using the RPM (see Section 2.1.1).\textsuperscript{4} The ROIs over which attenuation coefficients were estimated were set in two ways; 1) over all three layers, 2) within each layer. The RPM uses the ratios of power spectra from the sample to that from the reference at the same depth throughout the ROI. Based on the change of these ratios with depth, and assuming a constant backscatter coefficient, it estimates the attenuation coefficient (dB/cm) for each frequency component. Depending on the sample’s characteristics, the attenuation coefficients can have different frequency dependencies. However, in this study the attenuation coefficients were adequately fit to a linear function of frequency, and the slope of the attenuation coefficient vs. frequency was obtained for each layer of the every phantom. The result was then compared to the laboratory measurement result.

To calculate power spectra from the sample and the reference, a Hann window was applied to the RF echo data and this window was allowed to be overlapped. For the ROI covering all three layers, a window size of 5mm (13-pulse lengths for both transducers) was used, while the ROI for measurements of attenuation within each layer used a window size of 5mm for layer 1 and 3mm (8-pulse lengths for both transducers) for layers 2 and 3. Adjacent windows overlapped by 75% of the window size, both axially and laterally. The power spectrum from each window was averaged with those from adjacent beamlines at each depth to reduce the statistically random noise. Power spectra were computed by averaging periodograms for four uncorrelated adjacent beamlines (5mm laterally) for the data from the 18L6 transducer and three beamlines for the 9L4 transducer. The slope of the attenuation coefficient vs. frequency (“$\alpha_o$”)
was obtained from “attenuation estimation blocks.” The size of the attenuation estimation block was 8mm (axially) by 5mm (laterally) for the ROI consisting of all three layers, 8mm (axially) by 5mm (laterally) for layer 1, and 6mm (axially) by 5mm (laterally) for layers 2 and 3. The overlap ratio of attenuation estimation blocks was 85% for the three-layer ROI, 85% for layer 1, and 0% for layers 2 and 3.

4.2.5. Backscatter coefficient estimation

The BSCs were estimated as a function of frequency using the reference phantom technique 4 (see Section 2.3) applied to the RF echo signals acquired by the clinical system. This was done using both linear array transducers. The power spectrum was calculated in the same way as that used for attenuation estimations. The window size and overlap ratio were also kept the same. The ratio of the echo signal power spectrum from the sample to that of the reference phantom was obtained at each depth. The power spectra were then corrected for the difference between the attenuation losses along the sample path and the reference phantom path at each depth using the slope of the attenuation coefficient vs. frequency for each layer estimated by the laboratory measurement presented in Table 4.1. Using the known backscatter coefficients of the reference phantom, the backscatter coefficient as a function of frequency in each layer of the three phantoms was estimated (Eq. (2-15) in Section 2.3). The backscatter coefficients obtained from each spectral window over the region of interest were spatially averaged and presented as a function of frequency. For theoretical predictions of BSCs in three phantoms, the Faran’s scattering theory (see Section 2.2) 6 was used and the predictions computed with the phantom properties presented in Table 4.1, were compared with the estimated BSCs.
4.3 Results

4.3.1. Slope of attenuation coefficient vs. frequency

The estimated slopes of the attenuation coefficient vs. frequency from the three layers of “VBSC-24µm” are presented, along with the laboratory estimates in Fig. 4.3. Fig. 4.3 (a) and (c) show 2-D attenuation maps covering all three layers of the VBSC-24µm phantom from the data acquired with 18L6 and 9L4 transducers, respectively. Figures 4.3 (b) and (d) present plots of the attenuation coefficient vs. depth, obtained by averaging laterally the results from the 2-D attenuation maps of Figs. 4.3 (a) and (c), respectively. The red line in Fig. 4.3 (b) and (d) represents the laboratory attenuation measurements on the test sample pertaining to each layer. As expected, the attenuation estimates done by applying the RPM creates erroneous results for locations corresponding to the interfaces where the BSC changes. The RPM assumes a constant BSC over the ROI. The estimates from both linear array transducers show a similar error trend, although the boundary errors from the 9L4 transducer are a little higher than ones from 18L6 transducer.

The attenuation estimates of the VBSC-49µm phantom and the VA phantom are presented in the same manner in Figs. 4.4 and 4.5, respectively. The results from the VBSC-49µm phantom are similar to those from the VBSC-24µm phantom in Fig 4.3. Similar to the results in Fig 4.3 b) and d), the attenuation estimates exhibit a high degree of accuracy within the constant BSC sections. In contrast, for the VA phantom results in Fig 4.5, the attenuation estimates by the RPM showed good agreement with laboratory measurements over all three
layers, although the 18L6 transducer results in layer 3 and the 9L4 transducer results in layer 2 under-estimate the actual attenuation coefficients.

Figure 4.3. Estimated slopes of attenuation coefficient vs. frequency from the “VBSC-24µm” phantom using RPM: (a) 2-D attenuation map (18L6 transducer) (b) laterally averaged attenuation estimates, compared with the laboratory measurements (18L6 transducer) (c) 2-D attenuation map (9L4 transducer) (d) laterally averaged attenuation estimates, compared with the laboratory measurements (9L4 transducer)
Figure 4.4. Estimated slopes of attenuation coefficient vs. frequency from the “VBSC-49µm phantom” using RPM: (a) 2-D attenuation map (18L6 transducer) (b) laterally averaged attenuation estimates, compared with the laboratory measurements (18L6 transducer) (c) 2-D attenuation map (9L4 transducer) (d) laterally averaged attenuation estimates, compared with the laboratory measurements (9L4 transducer)
Figure 4.5. Estimated slopes of attenuation coefficient vs. frequency from the “VA phantom” using RPM: (a) 2-D attenuation map (18L6 transducer) (b) laterally averaged attenuation estimates, compared with the laboratory measurements (18L6 transducer) (c) 2-D attenuation map (9L4 transducer) (d) laterally averaged attenuation estimates, compared with the laboratory measurements (9L4 transducer)

The estimated slopes of the attenuation coefficient vs. frequency from each section of the three layered phantoms are presented in Table 4.2. The percent error with respect to the laboratory estimate is presented in the parenthesis. The minimum and maximum percent errors from the “VBSC-24µm” phantom are 1.9% and 15.4%. The VBSC-49µm phantom and the VA
phantom had similar percent error ranges of 0% and 8.5% for the minimum and maximum percent error, respectively. The mean percent error across the three layers, incorporating results from both transducers, was a bit higher in the case of the VBSC-24µm phantom (6.7%) than for either the VBSC-49µm phantom (4.9%) or the VA phantom (4.0%). However, as shown in the results all exhibited comparable errors.

4.3.2. Backscatter coefficient vs. frequency

The BSC as a function of frequency for the VBSC-24µm phantom, the VBSC-49µm phantom, and the VA phantom are presented in Figs. 4.6, 4.7, and 4.8, respectively. To analyze the variation of estimates, two quantities were computed:

a) Percentage Difference with respect to Faran ($\%D_{Faran}$): We computed the absolute value of the difference between the BSC estimate ($\eta_{Transducer}(f)$) from the 18L6, 9L4, and single element transducers and the Faran prediction ($\eta_{Faran}(f)$) at the same frequency, normalized over the predicted value. This is expressed as

$$\%D_{Faran}(f) = \left| \frac{\eta_{Transducer}(f) - \eta_{Faran}(f)}{\eta_{Faran}(f)} \right| \times 100.$$  \hspace{1cm} (4-1)

b) Percentage Difference with respect to the mean of BSC estimates from all transducers ($\%D_{Mean}$): This is defined as the absolute difference between the BSC estimate from
an individual transducer and the mean computed from the results of all transducers \( (\eta_{\text{Mean}(f)}) \) at the same frequency, normalized over the mean. That is,

\[
\% D_{\text{Mean}}(f) = \frac{|\eta_{\text{Transducer}}(f) - \eta_{\text{Mean}}(f)|}{\eta_{\text{Mean}}(f)} \times 100.
\] (4-2)

The overlapped frequency range of all transducer data was determined for each layer of phantoms. The computed quantities of (4-1) and (4-2) over the overlapped frequency range were averaged and presented in Table 4.3.

**Table 4.2.** Slope of attenuation coefficient vs. frequency estimates for each layer of layered phantoms. The presented value was obtained by averaging estimates from different \( \alpha \)-estimation blocks and frames. The value in the parenthesis is the percent error.

<table>
<thead>
<tr>
<th>Phantom</th>
<th>Transducer</th>
<th>Slope of attenuation coefficient vs. frequency (dB/cm-MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>layer 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(dB/cm MHz)</td>
</tr>
<tr>
<td>VBSC-24µm</td>
<td>18L6</td>
<td>0.48 (7.7%)</td>
</tr>
<tr>
<td>VBSC-24µm</td>
<td>9L4</td>
<td>0.49 (5.8%)</td>
</tr>
<tr>
<td>VBSC-49µm</td>
<td>18L6</td>
<td>0.49 (4.3%)</td>
</tr>
<tr>
<td>VBSC-49µm</td>
<td>9L4</td>
<td>0.49 (4.3%)</td>
</tr>
<tr>
<td>VA</td>
<td>18L6</td>
<td>0.48 (0%)</td>
</tr>
<tr>
<td>VA</td>
<td>9L4</td>
<td>0.50 (4.2%)</td>
</tr>
</tbody>
</table>
Table 4.3. Average values of $\%D_{\text{Faran}}$ and $\%D_{\text{Mean}}$ over the specified frequency range for the estimated BSC; (a) VBSC-24µm, (b) VBSC-49µm, (c) VA

(a) VBSC-24µm

<table>
<thead>
<tr>
<th>Transducer</th>
<th>Layer 1 (4-9.9MHz)</th>
<th>Layer 2 (4-8MHz)</th>
<th>Layer 3 (5-7MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$%D_{\text{Faran}}$</td>
<td>$%D_{\text{Mean}}$</td>
<td>$%D_{\text{Faran}}$</td>
</tr>
<tr>
<td>18L6</td>
<td>19.8</td>
<td>12.4</td>
<td>42.3</td>
</tr>
<tr>
<td>9L4</td>
<td>22.5</td>
<td>15.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Single element</td>
<td>23.1</td>
<td>27.4</td>
<td>20.3</td>
</tr>
</tbody>
</table>

(b) VBSC-49µm

<table>
<thead>
<tr>
<th>Transducer</th>
<th>Layer 1 (5-6.9MHz)</th>
<th>Layer 2 (4-8MHz)</th>
<th>Layer 3 (5-6.9MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$%D_{\text{Faran}}$</td>
<td>$%D_{\text{Mean}}$</td>
<td>$%D_{\text{Faran}}$</td>
</tr>
<tr>
<td>18L6</td>
<td>25.4</td>
<td>4.1</td>
<td>19.0</td>
</tr>
<tr>
<td>9L4</td>
<td>26.6</td>
<td>3.5</td>
<td>22.8</td>
</tr>
<tr>
<td>Single element</td>
<td>40.0</td>
<td>7.2</td>
<td>50.1</td>
</tr>
</tbody>
</table>

(c) VA

<table>
<thead>
<tr>
<th>Transducer</th>
<th>Layer 1 (4-9.9MHz)</th>
<th>Layer 2 (4-8MHz)</th>
<th>Layer 3 (5-6.9MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$%D_{\text{Faran}}$</td>
<td>$%D_{\text{Mean}}$</td>
<td>$%D_{\text{Faran}}$</td>
</tr>
<tr>
<td>18L6</td>
<td>1.7</td>
<td>10.4</td>
<td>9.6</td>
</tr>
<tr>
<td>9L4</td>
<td>5.9</td>
<td>6.2</td>
<td>8.9</td>
</tr>
<tr>
<td>Single element</td>
<td>23.5</td>
<td>15.8</td>
<td>13.5</td>
</tr>
</tbody>
</table>
Figure 4.6. BSC estimates for the “VBSC-24µm phantom”: (a) layers 1 and 3, (b) layer 2

Figure 4.7. BSC estimates for the “VBSC-49µm phantom”: (a) layers 1 and 3, (b) layer 2
Based on Table 4.3, the maximum value of $\%D_{\text{Faran}}$ was 77.6% from the estimate for the layer 3 of VBSC-24μm phantom using the 18L6 trasnducer. The minimum value was 1.7% from the layer 1 of VA phantom using the 18L6 transducer. The mean value of $\%D_{\text{Faran}}$ for the array transducers was 28.5% which was comparable to 26.9% of single element transducer. $\%D_{\text{Mean}}$ varied from 3.5%-41.0% where the minimum value was from the layer of 1 of VBSC-49μm phantom using the 9L4 trasnducer and maximum value was from the layer of 3 of VBSC-24μm phantom using the single element trasnducer. The mean value of $\%D_{\text{Mean}}$ for all transducers was 24.4%. The results from the VA phantom showed better agreement in magnitude and frequency dependence of the BSC than ones from VBSC phantoms.

4.4 Discussion
The RPM has been shown to provide accurate results for attenuation and BSCs estimated for homogeneous regions. The focus of this study was assessments of the accuracy of attenuation and BSC measurements obtained by the RPM when the ROIs extended over inhomogeneous layers or were located distal to such layers. Three tissue-mimicking layered phantoms (VBSC-24µm phantom, VBSC-49µm phantom, and VA phantom) were utilized to mimic inhomogeneous tissue paths for the study.

In Figs. 4.3, 4.4, and 4.5, attenuation coefficients determined using the RPM exhibit high accuracy for data acquired from ROIs over the three layers of the phantoms, except near boundaries where the BSC changes. The boundary errors are expected because changes in backscatter can be interpreted as reductions in amplitude caused by attenuation. Thus, the RPM needs to be carefully applied to avoid these boundaries. Often such BSC changes can be easily detected by looking at brightness changes in corresponding B-mode image, and avoiding data from locations of backscatter changes. However, in cases of small in vivo lesions, applying the RPM only within regions where the BSC is constant can be challenging.

When the ROIs were set within each layer, the slopes of attenuation coefficient vs. frequency agree with results of laboratory measurements of attenuation done using single element transducers and narrow band substitution. These results were presented in Table 4.2. Overall the percent error varied from 0% to 15.4%, and the mean percent errors over the three layers were 6.7%, 4.9%, and 4.0% for the VBSC-24µm phantom, the VBSC-49µm phantom, and the VA phantom, respectively. Based on the results in Table 4.2, there were greater relative errors in the attenuation estimates from the distal layer of all three layered phantoms. Layer 1 has a thickness
of 4cm while the other two layers each have a thickness of 1.5cm. The total attenuation accumulated by layers 1 and 2 could have been large, resulting in a lower SNR in the echo signal data from the bottom layer compared to the data from the shallow layers. The difference in the scatter size distribution between the two VBSC phantoms did not affect the accuracy of attenuation estimations in this experiment.

The estimates of BSCs done using the Siemens imaging system and array transducers are in agreement with results of laboratory measurements (mean values of %D_{mean}: 24.4%) and results from the theoretical predictions(mean values of %D_{Faran}: 28.5%). There was a small offset between BSCs measured with the clinical and the lab systems and those predicted with theory, although BSCs vs. frequency agreed. The maximum %D_{Faran} and %D_{Mean} were from the layer 3 and this could have also related to a low SNR in the bottom layer as described above.

The 18L6 and 9L4 transducers produced comparable BSC estimates, the mean values of %D_{Faran} were 28.1% and 29.0%, respectively. The array transducers showed the highest mean %D_{Faran} value of 42.9% for the VBSC-49µm phantom while the lowest mean %D_{Faran} value of 17.8% for the VA phantom. For the VBSC-24µm phantom, the %D_{Faran} value was 24.9%. It seems that the phantom with backscatter change was more challenging than the phantom with attenuation change in BSC estimation. Between two VBSC phantoms, the phantom with smaller scatterers produced more errors. That could be because the VBSC-24µm phantom had lower BSCs than the VBSC-49µm phantom and generated weaker echoes with lower SNR.

4.5 Conclusion
The slopes of attenuation coefficient vs. frequency from a clinical imaging system showed good agreement with laboratory measurements for layered tissue-mimicking phantoms. The BSC estimates for each layer were in agreement with laboratory measurements as well as with theoretical predictions in spite of a small magnitude offset. This study demonstrates that attenuation and backscatter measurements from layered media can be accurately estimated with a clinical imaging system that provides RF echo data.

4.6 References


Chapter 5: 
Quantitative ultrasound imaging in animal breast tumor models: fibroadenomas

Portions of this chapter are being published as:
This was a multi-laboratory experiment and K Nam was responsible for the Siemens S2000 studies.

5.1 Introduction

Several laboratories are developing and testing QUS techniques to differentiate tumor types *in vivo*. To date, success has been demonstrated in the case of identifying ocular tumors with QUS\(^1,2\) as well as prostate tumors.\(^3,4\) These studies show the potential of QUS for the identification and discrimination of tumors *in vivo*. For QUS estimates to translate to the clinic, it is imperative to be able to demonstrate system independence. Interlaboratory comparisons allow for an assessment of measurement agreement among measurements by different groups and systems. Previous comparison studies have evaluated quantitative backscatter and attenuation for physical phantoms with known properties, including glass spheres with varying size distributions. When methods to account for system dependencies on echo data were applied, excellent agreement in measured values was demonstrated among different measurement systems and between laboratories.\(^5,6\) To demonstrate system independence in more weakly scattering media, i.e., media that scatter ultrasound more like soft tissue, two laboratory systems
were used to examine an agar-based phantom with embedded spheres also made of agar but of different density than the background.\textsuperscript{7} Backscatter results for this model measured by the two systems were also in good agreement with predictions from scattering theory (see Chapter 3).

The next logical step in these QUS measurement system comparisons is to progress to backscatter coefficient estimates for animal models. A preliminary study was reported\textsuperscript{8}, which demonstrated reasonable agreement among BSC in four spontaneous rat tumors.

The goal of the study presented here was to perform an interlaboratory comparison of BSCs measured using both single-element laboratory scanners and clinical scanners in an \textit{in vivo} tumor model. This study expanded upon the previous study\textsuperscript{8} by determining the attenuation for each individual tumor, allowing for appropriate attenuation compensation and estimating effective scatterer diameters (ESDs) from the data. Spontaneous rat fibroadenomas were used to provide a heterogeneous, uncharacterized material in which to test these techniques and compare across systems. Attenuation values, BSC, and ESD within the tumors were estimated using data from each system (with the exception of no attenuation estimates from the laboratory system), and results were compared. A functional ANOVA method was used for comparison of BSC estimates.

5.2 Methods

5.2.1. Animal model

The study was done by 3 laboratory groups, including UW-Madison, in the Bioacoustics Research Labs, at University of Illinois, Urbana-Champaign (UIUC). Four Sprague Dawley rats (Harlan Laboratories, Inc., Indianapolis, IN) with spontaneous mammary tumors were imaged.
This model results in primarily fibroadenomas with a smaller number of carcinomas. Because these tumors were spontaneous, the location, rate of growth and histological category, as assessed by a board-certified pathologist, varied from animal to animal. The experimental protocol was approved by the Institutional Animal Care and Use Committee (IACUC), at UIUC and satisfied all University and NIH rules for the humane use of laboratory animals.

5.2.2. Ultrasound imaging systems

Siemens Medical Systems cooperated in this study by arranging to have a Siemens S2000 (Siemens Medical Solutions USA, Inc. Malvern, PA) transported to the Bioacoustics Research Labs at UIUC. Thus, three clinical systems and one single-element laboratory system were used to image the rat tumors. The three clinical systems were an Ultrasonix RP (Ultrasonix Medical Corporation, Richmond, BC); a Zonare Z.one scan engine diagnostic system (ZONARE Medical Systems, Inc, Mountain View, CA); and the Siemens Acuson S2000. For each system, the individual transducers used and their nominal center frequencies are summarized in Table 5.1.

Table 5.1. All transducers used, their nominal excitation frequencies, approximate bandwidth covered by the transducers for each system, are summarized, along with the cutoff used to determine this bandwidth. The system operated by the author and others in UW group is indicated as bold.

<table>
<thead>
<tr>
<th>Ultrasound system</th>
<th>Transducer</th>
<th>Nominal excitation frequency (MHz)</th>
<th>Approximate combined bandwidth (MHz)</th>
<th>Bandwidth cutoff criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>UltraSonix RP</td>
<td>L9-4/38</td>
<td>5</td>
<td>2 to 8</td>
<td>-6dB</td>
</tr>
<tr>
<td></td>
<td>L14-5/38</td>
<td>7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zonare Z. one</td>
<td>L8-3</td>
<td>7</td>
<td>4 to 9</td>
<td>-20dB</td>
</tr>
<tr>
<td>Ultrasound system</td>
<td>Transducer</td>
<td>Nominal excitation frequency (MHz)</td>
<td>Approximate combined bandwidth (MHz)</td>
<td>Bandwidth cutoff criterion</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------</td>
<td>------------------------------------</td>
<td>--------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Siemens Acuson</td>
<td>L14-5sp</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9L4</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S2000</td>
<td>18L6</td>
<td>15</td>
<td>2 to 14</td>
<td>10dB higher than noise floor</td>
</tr>
<tr>
<td></td>
<td>4V1</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory system</td>
<td>3.5 MHz (f/3)</td>
<td>3.5</td>
<td>0.6 to 10.5</td>
<td>-6dB</td>
</tr>
<tr>
<td></td>
<td>7.5 MHz (f/4)</td>
<td>7.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.2.3. Animal handling

The study was performed at the UIUC to enable sequential data collection from each animal with each system. In an experiment, the rat was anesthetized with 87mg/kg of ketamine hydrochloride and 13mg/kg of xylazine intraperitoneally. The hair over the tumor was shaved and depilated. A rectangular 20mm by 4mm box was drawn on the skin over the tumor region to indicate the region where data were to be acquired. A small piece of duct tape was placed in the upper left corner of the box to aid in positioning the imaging probes to coincide with the box and allow equivalent region of interest location among imaging systems. The rat was mounted in a custom holder and placed in a tank of room temperature degassed water. Data were acquired from each scanner without moving the rat relative to the holder. The linear array probes used in this study were offset from the skin surface by up to 2cm. For the lab scanning system the
transducer was positioned so that the focal distance was mid tumor. Images were acquired from a total of five planes separated by 1mm.

Tumors were scanned by each imaging system in varying (pseudo-random) order to avoid any biases that may arise based on the length of time under anesthesia. Total scanning time for an individual tumor with all four systems was approximately three hours; anesthesia level for each rat was carefully monitored by a UIUC veterinarian. After imaging, the animals were euthanized and the tumors were excised and sent to pathology for diagnosis.

5.2.4. Reference techniques

For the three clinical systems, reference scans were acquired from a well-characterized reference phantom using the same experimental settings as were used for the tumor data. The reference phantom was made with 6.4g of 5-43µm diameter glass spheres uniformly distributed in a 1600cc gel background material. The gel background material was an emulsion containing 70% safflower oil. The top of the phantom was covered with a 25µm-thick Saran wrap® (Dow Chemical, Midland, MI, USA). Acoustic properties of the reference were determined using a lab based narrow-band substitution method, applying it to material in “test cylinders” manufactured at the same time as the phantom. The sound speed was 1492m/s at 2.5MHz. The attenuation of the reference was determined experimentally using an insertion-loss technique using single-element transducers. A polynomial was fit to the data to approximate the frequency-dependent attenuation coefficient and is represented by the function $\alpha = 0.033 f^2 + 0.26 f + 0.18$, where $f$ is in MHz and $\alpha$ is in dB/cm. This function is estimated for the frequency range from 2 to 10MHz.
For the laboratory system, a reference scan was acquired from a planar Plexiglas reflector (with a pressure reflection coefficient of 37%) that was stepped through the entire depth of field of the transducer in quarter wavelength steps.

5.2.5. Attenuation

For each of the three clinical systems, the attenuation coefficient as a function of frequency of each tumor was estimated from the backscatter signal data. The data from the laboratory system were too noisy to extract attenuation estimates, and therefore no attenuation data were available from this system. A reference phantom technique\textsuperscript{9,12} that uses the spectral difference algorithm\textsuperscript{13-14} was implemented independently by each research group and was used to estimate the attenuation (see Section 2.1.1).

In all cases, the spectral ratios of the tumor region to reference at equivalent depths were computed to account for the system-dependent factors, including the ultrasound field, of the sample data. First B-mode images were constructed from the RF data by intensity modulating images according to the echo amplitude. Using the image, an overall region of interest (ROI) was chosen within the tumor where the tissue appeared to be homogeneous, to meet the uniform scattering assumption of the spectral difference method. Within the ROI, overlapping “windows of analysis,” as specified in each instrument-respective section below, were used to analyze power spectra as a function of depth. (see Table 5.2).
Table 5.2. Parameters used by each imaging system are summarized. The system operated by UW group is indicated as bold.

<table>
<thead>
<tr>
<th>Ultrasound system</th>
<th>Analysis window size</th>
<th>Analysis window overlap</th>
<th>Windowing function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Axial</td>
<td>Lateral</td>
<td>Axial</td>
</tr>
<tr>
<td>UltraSonix RP</td>
<td>15λ</td>
<td>50 scan lines</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>(7.5mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zonare Z.one</td>
<td>5 pulse lengths (0.847 mm for</td>
<td>Width of tumor (3.7 to 11.5 mm)</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>the L14-5sp and 0.524 mm for</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>the L8-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siemens</td>
<td>3 mm (3.9 μs)</td>
<td>3 mm (24-30 scan lines)</td>
<td>75%</td>
</tr>
<tr>
<td>Acuson S2000</td>
<td>Additional info</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ROIs varied in spatial extent, but were based on the available homogeneous region within tumors, as judged from gray scale images. An autocorrelation analysis of the RF echo data from the reference phantom was used to determine the amount of independent data within these 3 mm x 3 mm analysis windows. Using the distance over which correlation in the RF data dropped 20 dB as a metric, the average axial extent of the analysis window (among the three transducers) was nine “pulse-durations”, and the average lateral extent was 3.8 de-correlated “pulse-echo beam widths.” The power spectrum for each analysis window within the ROI of the tumor as well as within the reference phantom was estimated by applying a Hann window to each 3.9 μs scan line signal segment, doing a chirp-z transform, and then averaging laterally across the analysis window.

Power law fit

For each tumor, attenuation coefficient estimates from all three systems were plotted in dB/cm versus frequency. A power law of the form of
\[ \alpha = \alpha_0 f^n \]  

(5-1)

was fit to the data from all three systems using non-linear least squares fit.

### 5.2.6. Backscatter coefficients

For each system, the BSC as a function of frequency was computed for each tumor. The ROI within the tumor was outlined within each 2-D slice and divided into analysis windows, with sizes outlined in Table 5.2, to allow for the BSC estimates to be made locally and provide information regarding spectral variations when the ESDs are estimated.

For each of the three clinical systems the BSC was estimated using the reference phantom technique (see Section 2.3). For each analysis window, the ratio of the echo signal power spectrum from the sample to that of the reference \((PS_{\text{samp}}/PS_{\text{ref}})\) was estimated. The power spectra were then corrected for the difference between the attenuation of the reference phantom and the tumor at the depth of the analysis window, as determined by the power law fit. Eq. (2-14) in Section 2.3 was then solved for the BSC of the tumor tissue within the analysis window.

For all systems, the power spectrum from each individual scan line within the analysis window was averaged and used to then calculate the BSC. Estimated BSCs from all analysis windows within the ROI were averaged to produce the BSC for the entire slice (see Table 5.3).
Table 5.3. Specific analysis window size and overlap for each system. The system operated by UW group is indicated as bold.

<table>
<thead>
<tr>
<th>Ultrasound system</th>
<th>Analysis window size</th>
<th>Analysis window overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Axial</td>
<td>Lateral</td>
</tr>
<tr>
<td>UltraSonix RP</td>
<td>15 ( \lambda )</td>
<td>15 ( \lambda )</td>
</tr>
<tr>
<td>Zonare Z. one</td>
<td>5 pulse lengths (0.847 mm for the L14-5sp and 0.524 mm for the L8-3)</td>
<td>30 scan lines (2.57 to 4.78 mm)</td>
</tr>
<tr>
<td>Laboratory system</td>
<td>15 ( \lambda )</td>
<td>15 ( \lambda )</td>
</tr>
<tr>
<td>Siemens Acuson S2000</td>
<td>4 mm</td>
<td>4 mm</td>
</tr>
</tbody>
</table>

Additional Siemens Acuson S2000 info

The analysis windows used for the BSC were slightly larger than the analysis windows used in the Siemens data for attenuation coefficient estimations because the changes in the BSC with depth were not evaluated, which dictates using as small an axial region as practical. Power spectra were estimated in the same manner as for the attenuation analysis, with the frequency band chosen where all analysis windows exhibited values of the power spectrum at least 15 dB above the noise floor for the entire analysis frequency band. Within a given analysis window, at each frequency, the power spectrum value was divided by the spectral value from the reference phantom at the corresponding depth. Because the tumor-water interface was curved, the path through the tumor was estimated using the central acoustic scan line contributing to any analysis window, determining the top of the tumor to the center of the ROI along this line and applying attenuation corrections using Eq. (15) in Section 2.3.

**Laboratory system**

The entire visible portion of the tumor was outlined. Due to the fixed focus and often high attenuation, some regions of the tumor were not visible on a B-mode image and therefore were not included in the selected ROI. The analysis bandwidth was chosen as the -6dB width of the power spectrum from the Plexiglas reference at the focus. For each analysis region a reference power spectrum was obtained from the Plexiglas reflector by taking all reflections that corresponded to positions within the analysis window and averaging the spectra. The power spectra were estimated for all scan lines within the analysis window and divided by the average.
reference power spectrum. To compensate for attenuation on a per line basis the attenuation of water was used up to the surface of the tumor and then the power law fit of the attenuation for the individual tumor from the surface of the tumor to the mid-point of the windowed RF line. The BSC was then estimated using the method described by Chen et al.\textsuperscript{15}

*Spectral analysis*

A functional analysis of variance (ANOVA) was employed to compare the frequency-dependent BSC curves from different transducers. The method was based on works by Shen and Faraway\textsuperscript{16} and Cuevas et al.,\textsuperscript{17} for data in which the unit of observation is a function observed over a range of input values (frequencies) using both a large sample approximation and a Bootstrap method\textsuperscript{18} to evaluate significance. The method required the BSC functional responses to be analyzed over the same ranges of frequencies; therefore, BSC data were subdivided into frequency sub-regions determined by the bandwidths of the transducers to allow all transducers to be included in the analysis in at least one sub-region. It was necessary to run the analysis on several regions, as there was no frequency range that overlapped all the transducer bandwidths. A $p$-value of less than 0.05 was considered significant.

A root mean squared error (RMSE) of the $\log_{10}(\text{BSC})$ was also calculated to provide an estimate of the difference in BSC magnitude between different systems and transducers. In order to calculate the RMSE, the BSC for each transducer was averaged over all slices. Within the sub-region analyzed, corresponding to the same regions used in the functional ANOVA, data from all transducers were linearly interpolated to give data at the same frequencies for all datasets. The RMSE was calculated from the $\log_{10}(\text{BSC})$ data between all pairs of transducers because there
was no true value to compare against. The \( \log_{10}(BSC) \) was computed prior to calculating the RMSE as the BSC values are typically plotted on a log scale and therefore the relative shifts on a log scale have more intuitive meaning than the linear results.

### 5.2.7. Effective scatterer diameter estimates

ESD estimates were performed with one transducer for each imaging system to give overlapping bandwidth. The transducers employed for the ESD estimates were the Ultrasonix L14-5/38 transducer, the Zonare L8-3 transducer, the Siemens 9L4 transducer and the laboratory system 7.5MHz transducer. Estimates were performed using both the full bandwidth of each transducer and also with the bandwidth limited so that each transducer produced estimates from the same bandwidth. For the Zonare system, the limited bandwidth case was the same as the full bandwidth case.

The ESD was estimated for each ROI based on the Gaussian form factor (see Section 2.4). BSC is expressed in terms of the Gaussian form factor as,

\[
\sigma = f^4 \exp(-0.827ka^2)
\]  

(5-2)

where \( \sigma \) is BSC, \( f \) is frequency, \( k \) is the wave number and \( a \) is the scatterer radius. The ESD from the laboratory and Zonare systems were estimated by minimizing the mean square error (MSE) between the BSC and the form factor. The ESD from the Siemens and Ultrasonix systems were estimated based on closed form solutions detailed in the studies by Gerig, et al.\(^{19}\) (see Eq. (2-21) in Chapter 2) and by Oelze et al.\(^{20}\) respectively. Parametric images of both the ESD and
the corresponding MSE were constructed to provide information about the spatial distribution of scatterers. Where multiple analysis windows overlapped, the parametric image displays the average value.

In order to determine if there were statistically significant differences in ESD estimates across the imaging systems, an additive linear model with factor variables for rat, imaging system and bandwidth (full or limited) was run on the ESD data with $p$-values less than 0.05 considered significant. The method is a weighted least-squares with weights equal to the numbers of ESD estimates.

5.3 Results

The four tumors were histologically confirmed to be fibroadenomas. The diameters of the tumors ranged from 2cm to 4cm along the planes of image acquisition. Heterogeneity was observed both within individual tumors as well as between the four tumors imaged, as shown in the hematoxylin and eosin (H & E) stained histological images in Fig. 5.1. Tumor R3001 shows the greatest heterogeneities with the central region having less connective tissue than the surrounding tissue. Tumor R2993 is more fibrous than the other tumors.

5.3.1. Attenuation

Fig 5.2 shows the attenuation versus frequency plots for the four fibroadenomas with the power law, Eq. (5-1), fit to the combined data. Overlap was observed in the estimated attenuation values across the three clinical imaging systems (Zonare, Ultrasonix, and Siemens systems) with the data following a power law well over the extent of the frequency range. The power law
parameters are summarized in Table 5.4 with the power \( (n) \) ranging from 1.23 to 1.62, showing a deviation from linear frequency dependence of the attenuation. The local attenuation slope estimated at 7.5MHz from the power law fit is also summarized in Table 5.4 with high attenuation values observed from the four tumors (2 to 3.7dB/cm-MHz) and showing large variations between tumors. The individual fitted values for \( \alpha_0 \) and \( n \) were used for the attenuation compensation prior to computing the BSC.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>( \alpha_0 )</th>
<th>( n )</th>
<th>at 7.5MHz (dB/cm-MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R2993</td>
<td>0.56</td>
<td>1.62</td>
<td>3.2</td>
</tr>
<tr>
<td>R3001</td>
<td>1.15</td>
<td>1.40</td>
<td>3.7</td>
</tr>
<tr>
<td>R3017</td>
<td>1.04</td>
<td>1.41</td>
<td>3.3</td>
</tr>
<tr>
<td>R3018</td>
<td>1.05</td>
<td>1.23</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Table 5.4.** Coefficients for the power law fit to the fibroadenomas attenuation data in the form of \( \alpha = \alpha_0 f^n \). Estimated attenuation slope at 7.5MHz is provided for each tumor.
Figure 5.1. H&E stained slice of each of the four fibroadenomas, a) R2993 b) R3001 c) R3017 d) R3018. Left-side images are 4X (bar = 500 µm). Boxes in left-side images are the expanded images (40X, bar = 50 µm) on the right side.
Figure 5.2. The attenuation as a function of frequency is plotted for each tumor (a) R2993, (b) R3001, (c) R3017, (d) R3018. Axes and imaging system color code is consistent across all plots. The power law fit to the data is shown in black. The results by UW group are presented in various lines of red.

5.3.2. Backscatter coefficients

All transducers had considerable overlap in bandwidth with several other transducers allowing for a direct visual comparison of the BSC magnitude and trends when displayed graphically. Figs. 5.3(a)-(d) shows the BSC as a function of frequency for each of the four fibroadenomas. Both the individual slices of data and the averaged data for each transducer are
plotted to demonstrate the amount of variability within a tumor compared to the variability between transducers and imaging systems. A substantial amount of overlap is observed between multiple transducers, with the variability between systems and transducers being only slightly higher than the variability between individual slices obtained with a single transducer. Figure 5.3(b) for R3001 shows the greatest variability with the Siemens 18L6 and the Ultrasonix L14-5 showing a very different trend compared to the other transducers.

In order to perform the functional ANOVA and calculate the RMSE to compare across multiple transducers, relevant bandwidths needed to be selected for the analyses. The two frequency ranges that allowed for all transducers to be included in at least one range while keeping the bandwidth as wide as possible were 3.9 to 4.9MHz and 6.55 to 7.9MHz.

The functional ANOVA shows statistically significant differences across the BSC curves for all cases except for R3018 at the high frequency (6.55-7.9MHz) range. The RMSE between the log scaled BSC curves were computed for each pair of transducers over each of the two frequency ranges. The results are summarized in Fig. 5.4 showing the log (RMSE) for the comparison of both transducers within the same imaging system and between imaging systems over both the low and high frequency ranges used. The mean RMSE is less than 0.5 (log scaled) for all cases except for R3001 and R3017 at the higher frequency range.
Figure 5.3. The BSCs averaged across all slices and then BSC values for each individual slice are displayed for each tumor a) R2993, b) R3001, c) R3017, d) R3018. Axes and imaging system color code is consistent across all plots. The right-side plots represent BSC values from the individual slices. The results by UW group are presented in various lines of red.

Figure 5.4. Log RMSEs are shown for comparisons of data from transducers within the same imaging system and between imaging systems at both the low frequency and high frequency ranges analyzed. Error bars are the standard deviation across all pairs in that category, where no error bars are shown only one value was computed for that set. For the high frequency range R2993 and R3001 had one transducer per system and therefore there was no within comparisons.

5.3.3. Effective Scatterer Diameter
Fig. 5.5 shows an example of B-mode images of tumors, as well as the parametric ESD and MSE images for each imaging system. Variation in estimated ESD can be observed across the tumor with the general pattern of regions of higher and lower effective scatterer diameters being consistent across the different imaging systems. For the full bandwidth case, the bandwidth determined for each transducer was employed and is the same as was used in the preceding BSC estimates. The limited bandwidth range was selected as 3.6-6.6MHz, which is the region where the power spectra from all systems were above -20dB.

Results from the additive linear model showed statistically significant differences between the limited and full bandwidth case. Additionally significant differences were observed between rats, except for between R3017 and R3018 where no significant differences in ESD estimates were observed. After adjustment for animal and bandwidth there were significant system differences (p < 2x10^{-16}) between the Ultrasonix RP and the other three imaging systems. There are no significant differences between the ESD estimates from the laboratory, Siemens and Zonare systems.
Figure 5.5. B-mode images and parametric images of R3018 are shown as an example. First the Bmode image, followed by the ESD image and the MSE of the Gaussian fit for each imaging system a) Siemens, b) Zonare, c) laboratory system, d) Ultrasonix. The color map for the ESD values all range from 50 µm to 200 µm. The results by UW group are presented in the red box.
5.4 Discussion

Fibroadenomas are known to be very heterogeneous tumors, both within an individual tumor and between different tumors. The histological slices in Fig. 5.1 demonstrate the variations across the four samples imaged, including one tumor (R3001) that is highly heterogeneous within the sample. Despite local variations, the attenuation, BSC and ESD estimates agree well across all systems and transducers. The attenuation estimates agreed well across systems and fit well with the power law, allowing the measured attenuation for the individual tumor to be used to perform attenuation compensation prior to BSC estimation. The nonlinear frequency dependence of attenuation observed demonstrates the complex nature of the attenuation value that was consistently observed across systems.

Good agreement was observed among BSC estimates, even with limitations on obtaining data from the exact same region with every system. The ability to obtain consistent BSC estimates across systems, after appropriate attenuation compensation, is the cornerstone required to translate QUS techniques into clinical practice. The greatest variability in BSC was observed with tumor R3001 where the Siemens 18L6 and the Ultrasonix L14-5 showed a very steep slope at the upper end of their respective frequency ranges. While this trend does not fit with the trends from other transducers or even other slices of data obtained from the same transducers, it is interesting to note that the histology slides from this tumor (an example slide is shown in Fig. 5.1(b)) showed a greater heterogeneity than the other tumors with a central region that had more connective tissue than the surrounding tissue. It is possible that variations in regions where the
data were acquired could result in some data being acquired from a region with substantially different tissue properties.

Despite the differences in processing techniques, including the different types of references required between the single-element and array systems, differences in ROI sizes, system architecture and transducer characteristics, it was possible to maintain good agreement. This suggests that the obtained BSC is a fairly robust estimate and not particularly sensitive to the analysis parameters when properly accounted for. Room for improvement may lie within the experimental procedures to control for variations from one scan to the other and allow for more consistent data to be acquired.

The RMSE of log10(BSC) indicates that the average magnitude of the differences among measurements are typically quite small (within a factor of five). At this point, there is no clear choice of the best metric for comparing BSC values, or what the necessary level of agreement is to perform the desired analyses based on the BSC. Presented here is an extension of previous functional ANOVA methods to allow for the functional form of BSC data to be considered in evaluating the results. It will be an important consideration going forward to determine how to compare results between different imaging platforms.

The ESD estimate has demonstrated potential for distinguishing different types of tumors\textsuperscript{21, 22} and is presented here to demonstrate the consistency in estimates across systems. This is of particular significance as this is a parameter that could be used in clinical practice to aid diagnosis. The consistency in gradation of ESD estimates, including for the one system that showed significant differences, across the tumor presented indicates that there was sensitivity to
changes in properties that influence the ESD. It is interesting to note from Fig. 5.5 that the different orientations of the transducer relative to the tumor did not change the pattern observed for the lowest ESD estimates near the center of the tumor, suggesting this is likely a true result from the tissue rather than an artifact of the orientation.

5.5 Conclusion

In vivo imaging of rat fibroadenomas increases the level of complexity and heterogeneity considerably over tissue mimicking phantoms, yet, a reasonable level of agreement was observed in the attenuation, BSC and ESD estimates between all four imaging systems for the four different fibroadenomas studied. Variations in image acquisition and data processing techniques are still able to maintain comparable results, demonstrating that these measurements can be made in a system independent manner, which demonstrates the potential for clinical applications of QUS.

5.6 References


Chapter 6: 
Attenuation and Backscatter Coefficient Estimates of Rodent-Tumor-Mimicking Structures: Comparison of Results among Clinical Scanners

This chapter is published as:

6.1 Introduction

In recent years, the laboratories in University of Wisconsin-Madison, University of Illinois at Urbana-Champaign, and Iowa state university have jointly focused on demonstrating the feasibility of obtaining accurate and precise estimates of various quantitative ultrasound (QUS) parameters. Recent studies, including the study presented in Chapter 5, involved multi-system comparison of scanner-based $\alpha$ and $\eta$ estimates from in vivo spontaneous rat mammary fibroadenomas and implanted carcinomas. $^{1,2}$ General agreement was observed between attenuation values computed among four different systems, though the attenuation coefficients with clinical systems were significantly higher than those reported from a laboratory measurements using single-element transducers. $^3$ Root-mean-square errors among $\eta$ estimates from the four clinical imaging systems over the 4-5MHz range were as low as 5% for a fibroadenoma, but up to 330% for a carcinoma, although the frequency dependence of $\eta$
exhibited much better agreement. These differences were attributed mainly to spatial variations in properties of the masses, i.e., no single system scanned the exact same location of the tumor and at the exact orientation as another system. However, some of the variability might also be caused by differences in accounting for attenuation in masses as well as by other system- and analysis-dependent factors. Therefore, an essential step in the analysis of a multi-system study is to investigate the level of agreement independently of possible sample-related heterogeneity in the acquired data.

The goal of the work described in this chapter was to assess scanner-based $\alpha$ and $\eta$ estimates of well-characterized and homogeneous rodent-tumor-mimicking structures contained in a phantom designed to mimic conditions under which tumors in small mammals are often present and scanned. The intent was to determine whether the unusual geometry of the rodent tumor protruding above the body wall was causing our measurements (with all imaging systems) to be biased high. These estimates were generated by processing RF echoes from the phantom scanned with different clinical systems, emulating the data acquisition conditions and signal processing methodology used in the in vivo rodent-tumor characterization experiment cited above. In this chapter, estimates from four ultrasound imaging systems are compared to laboratory characterization of the acoustic properties of the rodent-tumor-mimicking structures as well as to predictions from Faran’s scattering theory for spherical scatterers.

6.2 Materials and Methods

6.2.1. Phantom design
The phantom emulates experimental conditions during rodent-lesion scanning,\textsuperscript{1,2} including a liquid path between the transducer and subject, a lesion protruding from the subject body forming a convex surface, and relatively high levels of ultrasound attenuation within the lesion compared to levels previously reported for such tumors.\textsuperscript{1-3} Following this idea, the phantom consists of three macroscopically uniform sections: two lesion-mimicking 1.6cm diameter spherical inclusions (referred to as Sphere A and Sphere B, see Fig. 6.1) protruding from a background in the shape of a rectangular parallelepiped. The phantom was fabricated using techniques reported previously.\textsuperscript{5} The phantom is immersed in a solution of water, propylene glycol and Liquid Germall Plus® (a preservative) and enclosed in an acrylic box.

![Figure 6.1. Side view (a) and top view (b) of the custom-made, rodent-lesion mimicking phantom.](image-url)
All three sections were composed of mixtures of water, agar, propylene glycol, and Liquid Germall Plus® as well as of different concentrations of graphite powder and different size distributions of glass-bead scatterers. Graphite powder concentrations were selected to achieve different levels of attenuation in each section. Attenuation coefficients were measured using substitution techniques, as described below. The glass bead scatterer size distribution (Fig. 6.2) for each phantom section was determined by measuring the diameter of 500 glass beads using a calibrated optical microscope. The physical characteristics of the spherical sections are shown in Table 6.1. The beads produce acoustic scattering and are spatially randomly distributed within each section. The different scatterer size distributions produce different frequency-dependent backscatter.

Figure 6.3 shows ultrasound B-mode images of (a) Sphere A and (b) Sphere B of the phantom, as well as (c) spontaneous mammary fibroadenoma in a live rat. The three images were acquired with the same system and transducer (Siemens S2000, 9L4, described below) as well as acquisition parameters. As can be observed, the experimental conditions and the gray-scale appearance of the rodent tumor are similar to those for the inclusions.
Table 6.1. Physical characteristics of the three sections in the phantom.

<table>
<thead>
<tr>
<th></th>
<th>Density (g/cm³)</th>
<th>Sphere mass (g) per unit volume (L) of agar/graphite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background (reference)</td>
<td>1.03</td>
<td>4.8g/ 1.2L</td>
</tr>
<tr>
<td>Sphere A</td>
<td>1.07</td>
<td>1.6g/ 0.4L</td>
</tr>
<tr>
<td>Sphere B</td>
<td>1.11</td>
<td>1.6g/ 0.4L</td>
</tr>
</tbody>
</table>

Figure 6.2. Glass-bead-diameter distributions of Sphere A and Sphere B determined by measuring the diameter of 500 glass spheres for each distribution using a calibrated optical microscope.
Figure 6.3. B-mode images of (a) Sphere A, (b) Sphere B, and (c) a spontaneous mammary fibroadenoma in a rat.² The three images were acquired with the 9L4 linear array transducer of the Siemens S2000 system under the same scanning parameters.

6.2.2. Acoustic properties of the phantom

2.5-cm thick test samples, formed of the materials making up each section of the phantom and poured at the time of its fabrication, were used in laboratory measurements of the attenuation coefficient α and speed of sound c of the three sections. Laboratory measurements of these properties were generated by applying a through-transmission narrow-band substitution technique,⁶ involving the transmission of 30-cycle acoustic pulses of different frequencies (2.5, 5, 7.5, and 10MHz) through the sample immersed in water. Pulses were emitted by a single-element unfocused transducer, traversed the sample, and reached a corresponding receiving transducer, whose signal was read by a digital oscilloscope (500MHz, Model LT342, LeCroy, Chestnut Ridge, NY). The amplitude change and temporal shift of the detected waveforms
compared to waveforms recorded in the absence of the sample were used to determine the attenuation and the speed of sound of the material in the sample, respectively. In the case of the speed of sound $c$, dispersion was neglected, and the average ± one standard deviation among values of the speed of sound determined at each transducer’s operation frequency is reported in Table 6.2. A power law fit was applied to the measured attenuation coefficient $\alpha$ (in dB/cm) vs. frequency,

$$\alpha(f) = \alpha_0 f^n,$$

(6-1)

to estimate the constant $\alpha_0$ (dB/cm-MHz$^n$) and the exponent $n$. Because the values of $n$ were close to 1, a linear fit was also applied to the data. The values from the linear fit were used for comparison with scanner-based $\alpha_0$ estimates as well as for attenuation compensation during the estimation of the backscatter coefficients from clinical imaging systems, described below. The results from these fits are presented in Table 6.2.

**Table 6.2.** Acoustic properties of the phantom. Speed of sound $c$ in m/s (average ± one standard deviation), attenuation coefficient $\alpha$ in dB/cm at 2.5MHz, parameters from a power fit and a linear fit to $\alpha$ versus frequency.

<table>
<thead>
<tr>
<th></th>
<th>$c$ (m/s)</th>
<th>$\alpha$ (2.5MHz) (dB/cm)</th>
<th>$\alpha_0$ (dB/cm-MHz$^n$)</th>
<th>$n$</th>
<th>$\alpha_0$ (dB/cm-MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background (reference)</td>
<td>1544± 1</td>
<td>1.06</td>
<td>0.36</td>
<td>1.17</td>
<td>0.51</td>
</tr>
<tr>
<td>Sphere A</td>
<td>1538± 3</td>
<td>2.51</td>
<td>0.97</td>
<td>1.02</td>
<td>1.02</td>
</tr>
<tr>
<td>Sphere B</td>
<td>1531±2</td>
<td>3.57</td>
<td>1.33</td>
<td>1.08</td>
<td>1.58</td>
</tr>
</tbody>
</table>

Test samples were also used in laboratory measurements of backscatter coefficients for the phantom components. These were performed using a broadband pulse-echo, planar reflector method and single-element focused transducers. The test samples and the transducer were immersed in a tank of degassed water at room temperature. The transducer was coupled to a computer-driven pulser-receiver (Model 5800, Panametrics, GE Inspection Technologies, Lewiston, PA). After placing the test sample at the focal plane of the transducer, a set of RF echoes was acquired by automatically moving the transducer (using an Aerotech Undex 11 motor displacer, GE Inspection Technologies, Lewiston, PA) in a plane parallel to the surface of the test sample in a raster fashion over 40mm x 40mm, at steps of 4mm. The RF signals were gated to consider only echoes from within the sample near the focal distance of the transducer. Echo signals from a planar quartz reflector, with its reflecting surface perpendicular to the pulse trajectory, were also acquired to account for the transmit-receive frequency response of the transducer-pulser-receiver system. Assuming a long duration gate, the backscatter coefficient is given by the ratio of the square modulus of the Fourier transform of the gated RF signal averaged over all the collected signals, divided by a term that accounts for the system’s frequency response, the shape of the gating function, and the transducer field integrated over the test sample volume. The procedure was performed using transducers with center frequencies of 3.5, 5.0, 7.5, and 10MHz to span the 2.4 to 12.9MHz range.
6.2.3. Data collection with clinical systems

Three laboratories participated in a cross-platform comparison of BSC estimation accuracy and each was aware of the attenuation properties of the three sections of the phantom as well as of the backscatter properties of the background, but not of the backscatter properties of the simulated masses. Each section was scanned with four clinical ultrasound systems: our Siemens Acuson S2000 (Siemens Medical Solutions USA, Inc, Malvern, PA) with 9L4 and 18L6 linear array transducers operated at 6 and 10MHz nominal excitation frequencies; an Ultrasonix RP system (Ultrasonix Medical Corporation, Richmond, British Columbia, Canada) with L9-4/38 and L14-5/38 linear array transducers operated at 5 and 7.5MHz nominal center frequencies by the group from the University of Illinois at Urbana-Champaign (UIUC); a Zonare Z.one scanner (Zonare Medical Systems, Inc, Mountain View, CA) with L8-3 and L14-5sp linear array transducers operated at 7 and 10MHz nominal center frequency by the group from Iowa State University (ISU); and a VisualSonics Vevo2100 (VisualSonics Inc., Toronto, Ontario, Canada) with a MS200 transducer operated at a 15MHz nominal center frequency also by the UIUC group. The scanners are equipped with research interfaces that supply either raw RF echo data or, in the case of the VisualSonics, quadrature data that permits reconstruction of the RF echoes. Data collection with all four systems took place during one scanning session at UIUC. RF echoes from five different image planes of each section of the phantom were obtained with each scanning system. During analysis, the background material of the phantom was used as a reference. Thus, RF data from all three sections scanned by each transducer were acquired using identical operator control settings and the same transducer-to-section distance.
6.2.4. Attenuation estimation

RF data from each system were processed by using the reference phantom method described in Section 2.1.1 to measure the attenuation coefficient.\textsuperscript{8} The general steps are the following: The spherical inclusion was identified in the B-mode image of each of the two-dimensional frames, and a region of interest (ROI) was defined within it. The ROI was subdivided into “\(\alpha\)-estimation blocks” whose sizes are shown in Table 6.3. An estimate of the attenuation coefficient was then obtained for each of these blocks. To do this, a block was further divided into a number of spectral estimation windows. Tapered segments of the RF echoes corresponding to each spectral estimation window were used to compute the power spectra from the sample and the reference. Windows were allowed to overlap both axially and laterally. The difference in depth dependence of the ratio of the sample to the reference power spectra was used to quantify the attenuation coefficient within each \(\alpha\)-estimation block. The size and amount of overlap between spectral windows and \(\alpha\)-attenuation blocks varied among systems, as presented in Table 6.3.

| Parameters used in the estimation of the attenuation coefficient (AL=acoustic line) |
|---|---|---|---|
| Ultrasonix | VisualSonics | Siemens | Zonare |
| Spectral window size (axial \(\times\) lateral) | 15-20\(\lambda\) \(\times\) 30-60AL | 4mm \(\times\) 4mm | 2.46mm \(\times\) 4.8mm |
| Spectral window overlap | 85% axially | 75% axially | 50% axially |
## 6.2.5. Backscatter coefficient estimations

The general procedure to estimate each spherical inclusion’s $\eta$ as a function of frequency from the RF data was the reference phantom method, using the phantom background (its laboratory-measured attenuation [Table 6.2] and backscatter coefficients) as reference.$^8,^9$ The following steps were performed:

1. A ROI was defined within the spherical inclusion based on the B-mode image of each acquired image plane. Multiple estimates of the power spectra from the sample and reference RF echoes were obtained within the ROI by placing a spectral analysis window at different locations within it. The specific window sizes, window overlap and bandwidth used for each system are listed in Table 6.4.
2. The frequency-dependent $\eta$ was estimated by applying the reference phantom method to the power spectra of the segmented RF echoes within the ROI. Neglecting multiple scattering and based on the fact that the speed of sound of the spherical inclusions and that of the reference phantom are similar (as shown in Table 6.2), the backscatter coefficient of the sample (spherical inclusion) $\eta_{\text{sample}}$ is obtained as follows:

$$
\eta_{\text{sample}}(f, z) = \eta_{\text{ref}}(f, z) \frac{S_{\text{sample}}(f, z)}{S_{\text{ref}}(f, z)} \exp \left[ -4 \int_0^z (\alpha_{\text{sample}}(f, \zeta) - \alpha_{\text{ref}}(f, \zeta)) \, d\zeta \right],
$$

(6-2)

where $\eta_{\text{ref}}$ and $\alpha_{\text{ref}}$ are the laboratory-measured attenuation and backscatter coefficients of the reference, and $S_{\text{sample}}$ and $S_{\text{ref}}$ are the echo signal power spectra from the sample and the reference phantom from a particular spectral analysis window. The exponential term corresponds to the compensation for the attenuation caused by structures above the spectral analysis window, which is at a depth $z_w$ from the transducer.

3. Backscatter coefficient estimates from each transducer were averaged over all spectral analysis windows within a ROI, and over the ROIs across different planes.
Table 6.4. Parameters used in the estimation of the backscatter coefficient.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ultrasonix</th>
<th>VisualSonics</th>
<th>Siemens</th>
<th>Zonare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectral window size (axial x lateral)</td>
<td>$15\lambda \times 15\lambda$</td>
<td>$15\lambda \times 15\lambda$</td>
<td>$4\text{mm} \times 4\text{mm}$</td>
<td>$2.46\text{mm} \times 4.8\text{mm}$</td>
</tr>
<tr>
<td>Spectral window overlap</td>
<td>85%</td>
<td>75%</td>
<td>75%</td>
<td>99%</td>
</tr>
<tr>
<td>Signal processing bandwidth (MHz)</td>
<td>L9-4: 3-6,</td>
<td>8-12.2</td>
<td>9L4: 4-10</td>
<td>L8-3: 3.1-7.2</td>
</tr>
<tr>
<td></td>
<td>L14-5: 3-8.6</td>
<td></td>
<td>18L6: 4-12</td>
<td>L14-5: 4.4-9.5</td>
</tr>
<tr>
<td>Bandwidth selection criterion</td>
<td>-12dB</td>
<td>-6dB</td>
<td>15dB above noise floor</td>
<td>-20dB</td>
</tr>
</tbody>
</table>

Analysis of $\eta$ estimates from each imaging system for the inclusions involved determining the level of agreement with theoretical predictions, which are calculated using the number density distribution of the glass beads and Faran’s theory for spherical scatterers. The theory requires the size, Poisson’s ratio, sound speed, and mass density of the glass beads as input parameters (see Section 2.2). Analysis also involved computing the variation of the estimates among different systems (including laboratory estimates), and assessing the similarity of the frequency dependence of the backscatter coefficient. To perform this analysis, the following quantities were defined:

c) Percentage Difference with respect to Faran ($\%D_{\text{Faran}}$): We computed the absolute value of the difference between the $\eta$ estimate from the clinical imaging system and
the Faran prediction at the same frequency, normalized over the predicted value. This is expressed as

\[
\% D_{\text{Faran}}(f) = \left[ \frac{\eta_{\text{System}}(f) - \eta_{\text{Faran}}(f)}{\eta_{\text{Faran}}(f)} \right] \times 100. \quad (6-3)
\]

d) Percentage Difference with respect to the mean of \( \eta \) estimates from all systems (%\( D_{\text{Mean}} \)): This is defined as the absolute difference between the \( \eta \) estimate from an individual system and the mean computed from the results of all systems at the same frequency, normalized over the mean. That is,

\[
\% D_{\text{Mean}}(f) = \left[ \frac{\eta_{\text{System}}(f) - \eta_{\text{Mean}}(f)}{\eta_{\text{Mean}}(f)} \right] \times 100. \quad (6-4)
\]

e) Effective Scatterer Diameter\(^{10}\): This was estimated through the minimization of the squared difference between the logarithms of the estimated backscatter coefficient and a theoretical model \( \eta_T(f) \) (in this case using Faran’s theory, updating the assumed scatterer diameter at each iteration of the minimization procedure) over a selected bandwidth.
\[ \hat{d} = \arg \min \frac{1}{N} \sum_{f \neq f_i} \left[ 10 \log \left( \frac{\eta(f)}{\eta_T(f; \hat{d})} \right) - 10 \log \left( \frac{\eta(f)}{\eta_T(f; \hat{d})} \right) \right]^2. \]  

(6-5)

Diameter search ranges were 15 to 55 µm for Sphere A, and 55 to 100 µm for Sphere B. Once the effective scatterer diameter was estimated, the similarity between \( \eta_T \) assuming the estimated effective scatterer diameter and the estimated \( \eta_{\text{System}} \) was quantified by computing the mean squared error, where the mean is taken over the \( N \) frequency points included in the analysis bandwidth:

\[ \text{MSE}(\eta_{\text{System}}, \hat{d}) = \frac{1}{N} \sum_{f \neq f_i} \left[ \eta_{\text{System}}(f) - \eta_T(f; \hat{d}) \right]^2. \]  

(6-6)

Due to the variability of transducer bandwidths and processing methods, the frequency bandwidths used for the \( \eta \) estimation varied among transducers as well as among systems. To perform the analysis of the fractional differences, overlapping sections of those bandwidths were selected. Two overlapping regions were identified: a low-frequency region from 4.9-6MHz (including estimates from all systems except the VisualSonics MS200), and a high-frequency region from 8-12MHz (including estimates from the 10MHz single-element transducer, Siemens 18L6 and the VisualSonics MS200). Then, \( \eta \) estimates from each system at the frequency points of the most coarsely sampled \( \eta \) estimate (Zonare 14L5 in the low-frequency region, and 10MHz single-element transducer in the high-frequency region) were obtained using linear interpolation.
from the original estimates. This procedure allowed us to have \( \eta \) estimates from all the systems within each overlapping region at the same frequency points.

The first [Eq. (6-3)] of the three quantities defined above [Eqs. (6-3)-(6-5)] aims at quantifying the discrepancy of each system’s \( \eta \) estimates with respect to predictions based on Faran’s theory, while the second one quantifies the variations with respect to the average trend of the experimental estimates. To simplify the analysis, the mean and standard deviations of the fractional differences over the low- and high-frequency ranges were computed. The third quantity is an approximate evaluation of the agreement in the frequency dependence of scattering among \( \eta \) estimates from the imaging system by assessing the effective scatterer diameter. The estimation of the scatterer diameters was performed using the interpolated \( \eta \) estimates within the low-frequency and high-frequency ranges defined above.

6.3 Results

Table 6.5 presents the estimates of \( \alpha_0 \) [Eq. (6-1)] assuming linear dependence on frequency \((n=1)\) for all scanners, as well as the laboratory estimates (presented also in Table 6.2). As observed, most of the estimates from clinical systems are in agreement with laboratory estimates. The average and maximum differences between systems with respect to the value from the laboratory measurement for Sphere A (1.02dB/cm-MHz) were 9% and 18%, respectively. The average and maximum differences for Sphere B (1.58dB/cm-MHz) were 12% and 29%. In general, Sphere B estimates had larger differences with respect to the expected
value. Furthermore, with the exception of one system, transducers with a higher nominal frequency range led to larger fractional differences.

**Table 6.5.** Laboratory and scanner-based estimates of the slope of the attenuation coefficient versus frequency \( \alpha_0 \) [Eq. (6-1)] assuming linear dependence on frequency \((n=1)\) for the spherical inclusions in the rodent phantom. Uncertainties indicate one standard deviation of attenuation results obtained from different frames.

<table>
<thead>
<tr>
<th>Scanning system</th>
<th><strong>( \alpha_0 ) (dB/cm-MHz)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Sphere A</strong></td>
</tr>
<tr>
<td>Laboratory</td>
<td>1.02</td>
</tr>
<tr>
<td>Siemens 9L4</td>
<td>1.00±0.05</td>
</tr>
<tr>
<td>Siemens 18L6</td>
<td>1.04±0.09</td>
</tr>
<tr>
<td>Ultrasonix L9-4</td>
<td>1.19±0.44</td>
</tr>
<tr>
<td>Ultrasonix L14-5</td>
<td>0.92±0.46</td>
</tr>
<tr>
<td>VisualSonics MS200</td>
<td>0.91±0.16</td>
</tr>
<tr>
<td>Zonare L8-3</td>
<td>0.98±0.08</td>
</tr>
<tr>
<td>Zonare L14-5sp</td>
<td>0.84±0.39</td>
</tr>
</tbody>
</table>

Figures 6.4 and 6.5 show backscatter coefficient vs. frequency results for the imaging systems from spherical inclusions A and B, respectively. Also shown are backscatter coefficients based on Faran predictions and those from the single-element transducer laboratory system. Figure 6.6 presents the mean (over frequency) values of the percentage differences with respect
to Faran predictions (lightly shaded bars) and to the mean of the experimental estimates (dark bars) for each imaging system’s backscatter coefficient. These were computed using Eqs. (6-3) and (6-4), respectively. Error bars indicate standard deviations among different frequency points. The number of frequency points used for the percentage difference calculations were 6 and 45 in the low- and high-frequency ranges, respectively. In general all the percentage differences, both with respect to Faran’s theory predictions and to the mean from all systems’ results, were comparable, the only exception being the L8-3 transducer on the Zonare system. Excluding results from this system, $\%D_{\text{Faran}}$ and $\%D_{\text{Mean}}$ of $\eta$ estimates for Sphere A and Sphere B were computed among systems. The average, minimum, and maximum values among these systems are presented in Table 6.6.

Table 6.6. $\%D_{\text{Faran}}$ and $\%D_{\text{Mean}}$ of $\eta$ estimates for Sphere A and Sphere B among all imaging systems and single-element transducers excluding the L8-3 transducer from Zonare system (average, minimum, and maximum values).

<table>
<thead>
<tr>
<th></th>
<th>Sphere A</th>
<th></th>
<th>Sphere B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$%D_{\text{Faran}}$</td>
<td>$%D_{\text{Mean}}$</td>
<td>$%D_{\text{Faran}}$</td>
<td>$%D_{\text{Mean}}$</td>
</tr>
<tr>
<td>Low-frequency range (4.9-6MHz)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>14</td>
<td>16</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Minimum</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Maximum</td>
<td>31</td>
<td>38</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>High-frequency range (8-12MHz)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results from the estimation of the effective scatterer diameter and the corresponding mean square error between the experimental backscatter coefficient and Faran theory predictions using the estimated effective scatterer diameter are presented in Table 6.7. For reference, the estimated effective scatterer diameter using the predicted backscatter coefficients shown in Figs. 6.4 and 6.5 is also presented; here values of 35.2µm and 34.7µm are obtained for Sphere A in the low- and high-frequency ranges, respectively, and of 85.9µm and 85.2µm for Sphere B for these same frequency ranges. Multi-system values for the mean ± one standard deviation of the estimated scatterer diameters within Sphere A and Sphere B were 45±12µm and 79±8µm in the low-frequency range, and 35±1µm and 77±1µm in the high-frequency range, respectively. With the exception of the value for Sphere A in the low-frequency range, these values are close to the upper and lower nominal limits of the expected scatterer diameter distributions in Sphere A and Sphere B, respectively. The standard deviation is related to differences in the frequency dependence of the estimated backscatter coefficient among systems. In general, larger deviations from the mean estimated scatterer diameter as well as larger values of the mean square error with respect to the Faran model used in the estimation corresponded to those systems that also exhibited the largest percentage differences of the estimated backscatter coefficient, reported in
Fig. 6.6. In addition, better agreement among systems was obtained in the high-frequency range. Dashed lines are presented in Table 6.6 in the cases where no convergence between the experimental backscatter coefficient and the theoretical model was obtained within the diameter search range.

Figure 6.4. Experimental estimates and theoretical predictions of the backscatter coefficient of Sphere A as function of frequency. (a) Laboratory characterization using single element transducers, (b) Siemens transducers, (c) Ultrasonix and VisualSonics transducers, and (d) Zonare transducers.
Figure 6.5. Experimental estimates and theoretical predictions of the backscatter coefficient of Sphere B as function of frequency. (a) Laboratory characterization using single element transducers, (b) Siemens transducers, (c) Ultrasonix and VisualSonics transducers, and (d) Zonare transducers.
Figure 6.6. Percentage differences between individual system estimates of backscatter coefficients, computed with respect to Faran predictions (%D_{Faran}) [Eq. (6-3)] and the mean backscatter coefficient from all systems (%D_{Mean}) [Eq. (6-4)]. Upper panel: Sphere A. Lower panel: Sphere B. Error bars indicate 1 standard deviation.
Table 6.7. Effective scatterer diameters ($d$) for glass spheres in Sphere A and Sphere B from backscatter coefficients measured by the different clinical systems. Also shown are mean square errors (MSE) for each system, with respect to the Faran’s theory model, assuming the estimated effective scatterer diameter. Dashed lines are assigned when no convergence was obtained in the minimization algorithm within the diameter search range.

<table>
<thead>
<tr>
<th>System</th>
<th>Sphere A</th>
<th>Sphere B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$d$ (µm)</td>
<td>MSE ($10^{-3}$)</td>
</tr>
<tr>
<td>Low-frequency range (4.9-6MHz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>From $\eta_{\text{Faran}}^a$</td>
<td>35.2</td>
<td>0.18</td>
</tr>
<tr>
<td>5.0MHz</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>7.5MHz</td>
<td>48.6</td>
<td>1.77</td>
</tr>
<tr>
<td>10MHz</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Siemens 9L4</td>
<td>49.7</td>
<td>1.87</td>
</tr>
<tr>
<td>Siemens 18L6</td>
<td>27.8</td>
<td>0.37</td>
</tr>
<tr>
<td>Ultrasonix L9-4</td>
<td>53.6</td>
<td>2.20</td>
</tr>
<tr>
<td>Ultrasonix L14-5</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Zonare L8-3</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Zonare L14-5</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>High-frequency range (8-12MHz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>From $\eta_{\text{Faran}}^a$</td>
<td>34.7</td>
<td>0.94</td>
</tr>
<tr>
<td>System</td>
<td>Sphere A</td>
<td>Sphere B</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>10MHz</td>
<td>35.9</td>
<td>76.7</td>
</tr>
<tr>
<td>Siemens 18L6</td>
<td>34.4</td>
<td>77.9</td>
</tr>
<tr>
<td>VisualSonics MS200</td>
<td>36.0</td>
<td>76.6</td>
</tr>
</tbody>
</table>

*Effective scatterer size was estimated using $\eta_{sex}$ based on glass-bead distributions (Fig. 5.2) and concentrations.*

### 6.4 Discussion

This study compares results of attenuation and backscatter coefficient estimates for components of a phantom designed to emulate challenges when performing QUS assessments of rodent tumors using clinical imaging systems. A total of eight linear array transducers from four systems were used to estimate the attenuation and the backscatter coefficient of the rodent tumor mimicking spheres in the phantom.

Most estimates of the attenuation coefficient generated using pulse-echo data from these systems were within 29% of narrowband through-transmission measurement values. The maximum discrepancy (29%) was measured for the highly attenuating Sphere B. A possible explanation for this finding is the considerable loss of SNR for RF signals from this mass. At 9MHz, the signal loss in Sphere B would be 14.2dB over 1cm (the diameter of the sphere is 1.6cm), which is more than 70% of the noise rejection level of 20dB. This suggests that in highly attenuating structures, there is a tradeoff in the slope-based estimation methods between the
ability to resolve the rate of decrease of the signal over depth and the increasing influence of noise in the estimates.

Results for the backscatter coefficients were, in general, consistent with predictions from Faran’s theory for the spherical scatterers distributed in the phantom sections. The percentage differences between measured results and predictions, $\%D_{\text{Faran}}$, and with respect to the mean estimate from all the systems, $\%D_{\text{Mean}}$, were similar among most systems indicating that the level of agreement among different systems and with laboratory measured values of the backscatter coefficient is comparable to the overall agreement with predictions. Furthermore, percentage differences for Sphere B were generally smaller than those for Sphere A. The largest percentage differences (not considering results from the Zonare L8-3 transducer) were about 33% with respect to predictions and corresponded to $\eta$ estimates for Sphere B in the high-frequency range. Interestingly, in this range the variability among systems was relatively small. This indicates that the results in this bandwidth may have been biased, which agrees with the observed underestimation at high frequencies in Fig. 6.5. A possible explanation of this result is the important loss of signal/noise caused by the high levels of attenuation at high frequencies.

In order to compare the frequency dependence of the backscatter coefficient derived from the different systems, we chose to fit each system's backscatter coefficient vs. frequency estimates to a scattering model (Faran’s theory), yielding an "effective scatterer diameter". Although each of the tumor mimicking spheres contains a range of scatterer diameters, as shown in Fig. 6.2, the effective scatterer diameter resulting from this analysis provides another means to assess levels of agreement among results for the different systems. Except for Sphere A in the
low-frequency range, reasonable agreement was obtained among the scatterer diameter estimates from different transducers. This discrepancy is likely due to the relatively small “\(ka\)” (product of the wave number and scatterer radius) for these scatterers at this frequency (\(ka = 0.39\) for 35\(\mu\)m-diameter scatterers at 5.5MHz); it has been shown that scatterer diameter estimation is ineffective for \(ka < 0.6\) (below which all scatterers behave as Rayleigh scatterers.\(^{11}\)) In the high-frequency range, estimated scatterer diameters for Sphere B were consistently smaller than the effective scatterer diameter predicted with Faran’s theory for the distribution of scatterer diameters. This agrees with the observed underestimation of the backscatter coefficient in Fig. 6.5 in this frequency range. The two different mean sizes in the spheres offer a reasonable contrast for this assessment and, in general, the scatterer diameter values obtained were consistent with the glass bead diameter distributions in each of the phantom’s spherical inclusions. The effective scatterer diameter values depend on the variation of backscatter coefficient with frequency, so in these determinations magnitude of the backscatter coefficients are less important. In addition, a smaller multi-system standard deviation in scatterer diameter estimates was obtained in the high-frequency range, which was derived from backscatter coefficient estimates from those transducers with higher frequency capabilities. These findings corroborate Insana and Hall’s assertion that effective scatterer diameter estimates improve, in most cases, with increasing signal bandwidth\(^{11}\) and with Gerig et al.’s statement about the possibility of reducing the variance of scatter diameter estimates by using high-frequency transducers.\(^{12}\) It is important to emphasize that a complete scatterer diameter analysis would require obtaining estimates at different locations within the region of interest in one frame and across independent frames to quantify the variance of each system’s estimate. In our case, the
estimation was performed using the final estimate of the backscatter coefficient from each system to make a comparison of the slope of the backscatter coefficient vs. frequency.

Although the intent was to standardize experimental procedures, some factors such as the variations in the location of the transducer over the sphere, differences in the frequency response of each of the transducers, or inclusion of (unnoticed) reverberations and clutter in the sample and/or reference RF data might have caused the small variations among estimates of the backscatter coefficient from imaging systems. Other factors contributing to estimate variance might have been differences in the system settings such as transmit power, gain and digitization methods, as well as the use of high transmit power that may lead to harmonic components in the detected signal, which up to now has not been strongly considered as a source of error in these measurements. Regardless of these factors, the overall agreement of the estimates of the backscatter coefficient is encouraging.

Differences in data processing techniques among different laboratories include variations in the location and size of the ROIs within the sample and the reference, variation in the spectral window size used to compute the power spectra as well as in the overlapping ratio of the sliding spectral analysis window, and different bandwidth selection criteria. It should be noted, however, that these differences did not result in major variability in attenuation results for one set of data. Specifically, the Siemens S2000 RF data were reanalyzed by the UIUC group using their specific data analysis approaches. Their resultant $a_0$ estimates were 0.95dB/cm-MHz for Sphere A and 1.71dB/cm-MHz for Sphere B, which are easily within the ranges found by the UW group, who originally processed this data set. We are completing a graphical user interface that will allow
analyzing RF data acquired from various imaging systems with a choice of signal processing method. The graphical user interface will facilitate testing data analysis strategies more thoroughly.

In spite of these variations, the overall ability of our laboratories to reproduce the frequency dependence of the backscatter coefficient from these samples is very encouraging.\textsuperscript{1,2,13} In addition, we emphasize that in this study, the variability in the estimation of the attenuation coefficient is not related to backscatter coefficient variability because laboratory-estimated attenuation values were used by all groups during attenuation compensation instead of each group’s slope estimates.

As a reference, we compared our results to those from the multi-system study performed by Wear \textit{et al.}\textsuperscript{13} Estimates of the attenuation coefficient from their phantoms A and B, with known attenuation properties (approximate slopes of 0.4 and 0.7dB/cm-MHz, respectively) were within 0.15 and 0.2dB/cm-MHz, which represent 38\% and 29\% of the expected values, respectively. In comparison, the maximum discrepancy of attenuation values found in this study was 29\%, even though the spherical inclusions had considerably higher attenuation coefficients than the Wear \textit{et al.} samples. Regarding the backscatter coefficients, Sphere A had a magnitude and frequency dependence similar to that in Wear \textit{et al.’s} Phantom B, while Sphere B in this study exhibited backscatter coefficient data similar to their Phantom A (as shown in Wear \textit{et al.’s} Fig. 4). In the first case (Sphere A vs. Wear \textit{et al.’s} Phantom B), multi-system variability between both studies was comparable. In the second case (Sphere B vs. Wear \textit{et al.’s} Phantom A), inter-system variability from Wear \textit{et al.} was larger (about two orders of magnitude) than the
results from the present study. The reason for the larger discrepancies found in the previous study can be attributed to the larger variability in data acquisition procedures (the phantoms were scanned at each laboratory instead of performing a joint scanning session), differences in $\alpha_0$ and $\eta$ estimation methods (each laboratory used their own estimation methods and reference phantoms or reflectors), as well as possible variations in composition of different samples of the phantoms.\(^{13}\) Therefore, the improved standardization of the procedures performed for the present study, particularly using the same sample and reference phantoms and scanning both of them during the same scanning session, helped in achieving better agreement among different groups.

It should be noted that although our results are sorted by measurement systems and transducers, this is not to suggest that specific errors, or particularly accurate results, are due to inherent properties of any of the systems. Rather, currently, QUS results still require understanding the limitations on accuracy imposed by algorithms, by system control settings, and by instrumentation specifications such as bandwidth. We are encouraged by the agreement exhibited among the results reported in this paper. Experiments of this type are important because they help uncover sources of error in QUS measurements and processing procedures, thereby leading to improved accuracy of the estimates. In the final analysis this will lead to improvements in medical ultrasound diagnoses.

One shortcoming of the present experiment may be in precisely representing any effects of speed of sound variations that may have been present in the $in vivo$ experiment. The presence of a water-alcohol solution path between the transducer and the phantom sections instead of pure water as in the $in vivo$ experiments might have led to two differences between the phantom and
the \textit{in vivo} scenarios. In the \textit{in vivo} case, the 22$^\circ$C water path had a speed of sound of 1490m/s, while in the phantom case the water-alcohol solution used to avoid damage of the phantom had a speed of sound of 1535m/s, which closely approaches the speed of sound in the phantom sections as shown in Table 6.2. Therefore, any possible refraction effects would have been reduced in the phantom experiment. Second, a difference in the speed of sound of water and tissue in the \textit{in vivo} experiments might have led to errors in the diffraction correction implicit in the reference phantom method used to estimate the attenuation and the backscatter coefficients. In spite of these differences, the two spherical inclusions of the phantom successfully resembled the shape as well as the attenuation and echogenicity of rodent tumors, as the B-mode images in Fig. 6.3 show.

Another shortcoming of this work is the lack of correlation between the error analysis in this study and the parameter estimation requirements for the specific task of breast tissue classification based on QUS analysis. While the studies reported here were necessary to reduce the suspicion of estimate bias in the inter-laboratory rodent tumor study,$^{1,2}$ this work does not provide estimates of the differences between QUS parameter values for various breast tissues. This work also does not yet provide guidance for the maximum QUS parameter estimate variance that would allow confident tissue classification. This work does, however, provide confidence that the parameter values estimated in our animal model work are accurate and can be used to guide studies in human subjects. Even with that, clinical trials with human subjects are necessary to investigate the utility of these techniques.

6.5 Conclusion
The present study has evaluated the accuracy of estimates of the backscatter coefficient and attenuation coefficient by various research groups using different clinical ultrasound equipment and scanning procedures set up for studying a preclinical tumor model. Most systems and transducers estimated attenuation coefficients within one standard deviation of the known value. When the known attenuation coefficient was used in the estimation of the backscatter coefficient, most systems correctly characterized the effective diameter of scatterers as long as $ka$ exceeded 0.6. Although there is still room for improvement regarding methodology standardization for some systems, the present results validate our procedures and encourage their further application in the characterization of in vivo lesions. In addition, this study shows the importance of performing methodology evaluations using well characterized phantoms that emulate subject scanning conditions to make progress in Quantitative Ultrasound.

6.6 References


Chapter 7:
Simultaneous Backscatter and Attenuation Estimation using a least squares method with constraints

This chapter is published as:

7.1 Introduction

We are applying quantitative ultrasound (QUS) for in vivo breast tumor diagnosis. The challenge for QUS in this application is related to the limited size of many breast masses and to the need to correct spectral data for attenuation along the (often heterogeneous) tissue path between the ultrasound transducer and the region of interest (ROI). Attenuation and viscous losses compete with scattering to affect the magnitude of detected echo signals. Furthermore, spatial variations in both properties complicate the use of simple reference techniques, such as the reference phantom method (RPM) developed by our group\(^1\) for accounting for both system dependencies of echo signal data and attenuation along the propagation path. Eliminating system dependencies in the data is desirable in QUS to obtain parameter estimates that are independent of the imaging system, and the use of a reference phantom is a popular and easy way to account for these system factors. Although reference phantom methods exhibit high accuracy when the ROI is homogeneous, in most in vivo breast cases, these conditions are not met.
To account for attenuation effects over an inhomogeneous pathway, Lu et al.\textsuperscript{2} proposed a dual-spectrum method and measured an “effective attenuation coefficient” of the body wall for backscatter studies in the liver. They assumed the frequency dependence of backscatter in the liver and in a reference phantom used in the method was unchanged over their analysis frequency range. Bigelow et al.\textsuperscript{3} introduced a Gaussian transformation algorithm and a Spectral fit algorithm to estimate both the total attenuation and the effective scatterer size. The technique yielded values of total attenuation to a region of interest that agreed to within 20% for some cases. To date the method has not been evaluated using array transducers.

The purpose of the work presented in this chapter is to describe a least squares method to estimate the effective attenuation between the ultrasound transducer and a ROI. The approach uses the power spectrum of RF echo signals from a ROI within the sample as well as the power spectrum acquired from the same depth in a well characterized reference phantom. The ratio of the spectra is fit to a 3-parameter tissue model that quantifies the attenuation and backscatter properties of the media. The least squares method is introduced in detail in the next section.

We also present results of phantom tests of the least squares method. Phantoms with depth varying attenuation and depth varying backscatter levels, as well as ones with uniform attenuation and backscatter, were constructed and studied with this technique.

7.2 Methods and Materials

7.2.1. Least Squares with constraints
The least squares method (LSM) is applied to echo signals from a region of tissue that are acquired following broadband excitation of an ultrasound transducer. Assuming the scattering in soft tissue is weak enough to ignore multiple scattering (first-order Born approximation) and the distance from the transducer to the ROI is greater than the transducer aperture, the power spectrum of the backscattered RF echo signals from the region can be written as

$$S(f, z) = G(f) \cdot D(f, z) \cdot A(f, z) \cdot B(f), \quad (7-1)$$

where $f$ denotes frequency and $z$ represents the depth of the region of interest. $S(f, z)$ is the power spectrum of the backscattered echo signal and $G(f)$ represents the combined transducer effects from transmitting and receiving an RF signal. $G(f)$ depends on factors such as the transducer design, pulsing characteristics and receiver gain. $D(f, z)$ accounts for beam forming and diffraction effects, $A(f, z)$ represents the total attenuation through the path from the transducer surface to the depth of interest, and $B(f)$ is the backscatter coefficient vs. frequency in the region of interest.

The cumulative attenuation $A(f, z)$ to depth $z$ is assumed to be spatially homogeneous with respect to the transducer surface. Furthermore, we assume attenuation can be approximated as having a linear frequency dependence, and so is modeled as

$$A(f, z) = \exp(-4\alpha f z), \quad (7-2)$$
where $\alpha$ is an effective attenuation coefficient vs. frequency slope for the propagation path.

Similarly, the backscatter coefficient $B(f)$ within the ROI is modeled as

$$B(f) = bf^n,$$  \hspace{1cm} (7-3)

where $b$ is a constant coefficient and $n$ expresses the frequency dependence.

Echo data also are acquired from a reference phantom whose backscatter and attenuation properties are well characterized, using the same transducer, transmit focus, and other equipment settings. Assuming the sound speed in the reference and sample media are the same (diffraction characteristics in these media are the same) the ratio of the echo signal power spectrum from the sample to that from the reference phantom at the same depth can be expressed as,

$$RS(f, z) = \frac{S_s(f, z)}{S_r(f, z)} = \frac{B_s(f) \cdot A_s(f, z)}{B_r(f) \cdot A_r(f, z)} = \frac{b_s f^n}{b_r f^n} \cdot \exp\{-4(\alpha_s - \alpha_r) f \cdot z\},$$ \hspace{1cm} (7-4)

where the subscripts $s$ and $r$ represent the sample and the reference phantom, respectively.

Taking the natural logarithm of both sides of Eq. (7-4), we get

$$\ln \frac{S_s(f, z)}{S_r(f, z)} = \ln \frac{b_s}{b_r} + (n_s - n_r) \ln f + 4(\alpha_s - \alpha_r) f \cdot z.$$ \hspace{1cm} (7-5)
To simplify Eq. (7-5), we substitute the following terms:

\[
\ln \frac{S_r(f,z)}{S_r(f,z)} = X(f,z), \quad \ln \frac{b_i}{b_r} = b, \quad n_i - n_r = n, \quad \alpha_s - \alpha_r = \alpha \quad (7-6)
\]

Then Eq. (7-5) can be written as

\[
X(f,z) = b + n \ln f - 4\alpha f z. \quad (7-7)
\]

To solve for the three unknowns, \(b, n,\) and \(\alpha\) in Eq. (7-7), a least squares fitting process is applied over the band of frequencies contained in the echo signal. That is,

\[
[\hat{b}, \hat{n}, \hat{\alpha}] = \arg \min_{b, n, \alpha} \sum_{i=1}^{K} (X(f_i,z) - b - n \ln f_i + 4\alpha f_i z)^2 \quad (7-8)
\]

where \(K\) is the number of frequency components to be used for the least squares fitting and \(\hat{b}, \hat{n}, \hat{\alpha}\) are the estimated parameters for the tissue model. Without loss of generality, Eq. (7-8) may be subjected to constraints to keep the result tenable. That is,

\[
b_1 \leq b \leq b_2, \quad n_1 \leq n \leq n_2, \quad \alpha_1 \leq \alpha \leq \alpha_2, \quad (7-9)
\]
with the search range of each parameter set according to expected ranges for the tissue or sample media within the ROI.

Realistic bounds easily can be made for the range of backscatter coefficients, attenuation coefficients, and frequency dependencies of backscatter allowed for the sample, as discussed below. Once \( b \), \( n \), and \( \alpha \) are estimated, the backscatter function and effective attenuation of the sample are computed using the known values for the reference phantom and Eq. (7-6).

### 7.2.2. Uniform phantoms

The LSM was evaluated first by recording echo signal data for two tissue-mimicking phantoms with uniform attenuation and backscatter. One was used as a reference (Phantom 1) and the other as the unknown sample (Phantom 2). Both phantoms were made with 1-45\( \mu \)m diameter glass bead scatterers randomly distributed in an oil-in-gelatin emulsion.\(^4\) The tops of Phantom 1 and Phantom 2 are covered with a 25\( \mu \)m thick Saran\textsuperscript{TM} film (Dow Chemical, Midland MI, USA) and a plastic coated aluminum foil (made by Gammex Inc., Middleton, WI, USA), respectively.

To establish values for acoustic properties of the reference phantom, and to allow estimates of the accuracy of the LSM, speeds of sound, attenuation coefficients, and backscatter coefficients were measured on test samples containing the phantom media. These test samples have two parallel transmission windows separated by a known distance. The test samples were made at the same time each phantom was manufactured. Narrow band substitution techniques\(^5\) were used to measure sound speeds and attenuation coefficients within the samples, while a
broadband reference reflector method\textsuperscript{6} was used to measure backscatter coefficients. The latter involves determining the echo signal power spectrum within the sample, determining the spectrum from a smooth planar interface, and modeling the 3-dimensional beam profile as well as the transmission and reception properties of the transducer-pulser-receiver used in the experiment. The accuracy of the Chen method has been reported previously.\textsuperscript{6}

The speed of sound within both phantoms is 1492m/s, as measured at 2.5MHz. Dispersion in the tissue mimicking materials is negligible, i.e., typically it has resulted in approximately a 3m/s increase in sound speed for a 20MHz frequency elevation.\textsuperscript{7} The measured attenuation from 2-10MHz was fit to a line to approximate a linear frequency dependence. Attenuation values for the reference phantom (Phantom 1) and the sample (Phantom 2) were 0.55dB/cm-MHz and 0.54dB/cm-MHz, respectively.

7.2.3. Phantoms with attenuation and backscatter contrast

We also applied the LSM to two tissue mimicking phantoms with spatial variations in backscatter and attenuation to test whether the method is sensitive to variations in backscatter and attenuation along the ultrasound beam paths. Phantom 3 (VBSC-24µm phantom in Chapter 4, see Fig. 7.1(a)), has three layers with equivalent backscatter coefficients, but with the middle layer having a higher attenuation coefficient than the other two layers. Phantom 4 (VA phantom in Chapter 4, see Fig. 7.1(b)) has three layers with nearly the same attenuation, but the middle layer has a 6dB higher backscatter coefficient than the other two layers. Both phantoms consist of water based gel with evaporated milk to control attenuation and nominally mean size of 35µm diameter glass spheres to provide scattering.\textsuperscript{8} The layered surfaces are bonded together, and
because the media are nearly identical in density and sound speed reflection losses at the interfaces are negligible.

Speeds of sound, attenuation coefficients, and backscatter coefficients for each layer were again measured using test samples manufactured during construction of the phantom. Identical lab techniques were applied as for Phantoms 1 and 2 to measure these acoustic properties. Properties of the phantom components are summarized in Table 4.1 (a) and (c).

![Figure 7.1](#)

**Figure 7.1.** Layouts of three-layer phantoms (BSC at 7MHz is shown here): (a) Phantom 3: the same BSC throughout, but with a higher attenuation in the middle layer, (b) Phantom 4: nearly the same attenuation coefficient throughout, but a higher BSC in the middle layer.

### 7.2.4. RF Data Acquisition and Analysis

To evaluate the accuracy of the LSM, phantoms were scanned using a Siemens Acuson S2000 system (Siemens Medical Solutions USA, Inc., Malvern, PA) equipped with a 9L4 (192 elements, 3 rows, 200µm element pitch) and an 18L6 (576 elements, single row, 100µm element
pitch) linear array transducer. The (nominal) excitation frequencies of the echo data were 9MHz and 10MHz for the 9L4 and 18L6 transducers, respectively. The Axius Direct ultrasound research interface on the Siemens system was used to acquire frames of RF data at a 40MHz sampling frequency. Each frame consisted of 456 and 368 acoustic scan line signals for 9L4 and 18L6 arrays, respectively. This was repeated for seven independent frames, each one acquired after an elevational translation or a rotation of the transducer in order to obtain statistically independent echo data.

The uniform phantoms and the layered phantoms were scanned at different times and with slightly different equipment settings, i.e., we did not reproduce time-gain compensation and overall gain settings from one experiment to another. However, since RF echo data also were taken from a reference phantom, it was possible to account for any differences in settings on the resulting echo signal spectra. To evaluate the LSM for uniform paths, Phantom 1 was used as a reference and Phantom 2 as the sample. With the layered phantoms, where attenuation or backscatter varied along the beam path, each phantom was scanned from the top as seen on the diagrams in Fig.7.1. In this case “reference phantom” data were taken from the top layer of Phantom 3 after rotating it 90° to gain access to this uniform volume.

The echo signal power spectra acquired from ROI’s in the phantoms were calculated by applying a Chirp-Z transform (CZT) with a 4mm long Hann window. Power spectra were evaluated from different regions over a 0.7-6.5cm (axial) by 0.5-3.3cm (lateral) area for each frame of echo data. The power spectra analysis windows were overlapped axially by 75%. This was done by incrementing the Hann window 1 mm along the beam path for successive spectral
calculations. A single power spectrum was then obtained at each depth by averaging data across acoustic beam lines and from the seven independent planes. For the Phantom 2 experiment the power spectra were corrected by multiplying by the transmission coefficient for the respective scanning windows of the sample and reference phantoms. With the layered phantoms the transducer could be placed in direct contact with the tissue-mimicking materials so no transmission corrections were applied as the coupling from transducer-to-phantom was the same in the sample and reference cases.

The constrained LSM was applied to compute total attenuation to the depth of analysis within the sample as well as the sample’s backscatter coefficient at that location. The following constraints were used for Phantom 2:

\[
10^{-7} \leq b_s \leq 10^{-1}, \quad 0 \leq n_s \leq 5, \quad 0.2 \leq \alpha_s (dB / cm - MHz) \leq 1 \quad (7-10)
\]

The possible attenuation coefficient values included in this analysis extend well beyond the ranges for the reference and sample phantoms involved. For the layered material phantoms, because the attenuation coefficient extended over a broader range than for the homogeneous phantoms, the upper limit of the allowable attenuation coefficient was set to 2dB/cm-MHz. Other values for the range of fitting parameters were the same as in Eq. (7-10).

Three equations in three unknowns were obtained by differentiating the right side of Eq. (7-8) with respect to each of the three variables and setting the derivatives to 0. These equations were then solved using the LSM. The frequency range applied in Eq. (7-10) varied with depth so
as to include only those frequency components that were at least 20dB above the noise floor. For shallow depths this extended from 3.7-7MHz while at the maximum, 6.5cm depth frequencies from 3.4-5.4MHz were employed.

For comparison with other methods applied to measure properties of tissues using clinical scanners, attenuation and backscatter coefficients also were measured for the sample phantoms by applying the RPM\(^1\) to the same spectral data. As reported by Yao et al.,\(^1\) the log of the ratio of the echo signal power spectra from the sample and reference are plotted as a function of depth, and the ratios are fit to straight lines. The slope of this line is proportional to the difference between the attenuation coefficients of the sample and reference phantom. The latter is known so this yields the attenuation coefficient of the sample. Then by substituting measured values and known quantities into Eq. (7-4), the backscatter coefficient of the sample can also be determined.

7.3 Results

7.3.1. Effective Attenuation Coefficients

Effective attenuation coefficient results generated by the LSM for uniform Phantom 2 are shown in Fig. 7.2. The “expected” values are those derived from the laboratory measurements. The RPM (see Section 2.1.1) yields an estimate for the “local” attenuation coefficient centered within the 8mm analysis windows. RPM results were converted to effective attenuation coefficients by summing overlying local attenuation increments to the analysis window and then dividing by the depth of the window. Because Phantom 2 is uniform, the effective attenuation coefficient equals the local attenuation coefficient throughout. The estimated attenuation coefficient results from the LSM and the RPM are in agreement with the expected values to
within 16.6%, with an average error of 4.0% and within 16.0% with average error of 6.9%, respectively.

![Effective attenuation](image)

**Figure 7.2.** Effective attenuation coefficients vs. depth results for Phantom 2 (a uniform phantom)

Results for the measured attenuation coefficients in the heterogeneous phantoms are shown in Figs.7.3 and 7.4. Here LSM-measured effective attenuation coefficients vs. depth are compared with results obtained using the RPM and with expected values obtained from laboratory measurements on test samples. Note, the values reported in these plots are the total attenuation to the ROI divided by the depth of the ROI, and hence are given in dB/cm-MHz. Since the transducer was in direct contact with the layered phantom and the path is uniform for
the first 4cm, the expected effective attenuation coefficient over this region is the same as the local attenuation coefficient. Then, beginning at 4cm, i.e., the depth of the interface between the top and middle layers, there is a gradual increase in the expected and measured effective attenuation coefficient values because of a greater attenuation within the middle layer contributing to the total attenuation to the ROI. In a like manner, the effective attenuation coefficient predictably decreases for points beyond the higher attenuating layer. Results from the RPM were interpreted as effective attenuation coefficients at each depth, as was done previously for Phantom 2. Since the local attenuation above the ROI could not be calculated due to low signal to noise ratio, the expected (independently measured) local attenuation value was used for effective attenuation coefficient calculations in the RPM results.
Figure 7.3. Effective attenuation coefficients results for Phantom 3 (constant backscatter)

![Effective attenuation](image)

Figure 7.4. Effective attenuation coefficients results for Phantom 4 (constant attenuation)

As can be seen in the Figs. 7.3 and 7.4, the estimated effective attenuation coefficients from the LSM are in good agreement with the expected values for both phantoms. The percent errors are presented in Table 7.1.

Higher errors were observed from both methods for Phantom 4, in which there is a variation in backscatter along the beam path. The performance of the LSM was comparable to the RPM results for Phantom 3. For Phantom 4’s results, the LSM produced an increased bias for
the first layer but less bias in the following layers than the RPM. The RPM method used the expected local attenuation value for effective attenuation coefficient calculations and therefore had no bias at the start of the ROI. Considering this advantage to the RPM results, the performance of the LSM for Phantom 3 and 4 was encouraging.

**Table 7.1.** Percent errors from effective attenuation coefficients results

<table>
<thead>
<tr>
<th></th>
<th>Maximum percent error</th>
<th>Mean percent error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Least squares</td>
<td>RPM</td>
</tr>
<tr>
<td>Phantom 3</td>
<td>6.3 %</td>
<td>5.3%</td>
</tr>
<tr>
<td>Phantom 4</td>
<td>16.2%</td>
<td>27.9%</td>
</tr>
</tbody>
</table>

When applying the RPM to the backscattered echo data, large errors in local attenuation estimations occurred at the layer boundaries of Phantom 4. The homogeneity of backscatter assumed in the RPM is violated at these interfaces, and the effects are vividly displayed in Fig. 7.5 where local attenuation coefficients vs. depth are shown. The high backscatter at the boundary results in an increase in apparent local attenuation at the proximal boundary and a decrease in the local attenuation at the distal boundary, relative to actual attenuation coefficients. The arrows in the figure indicate the boundaries of the layers.
Figure 7.5. Local attenuation coefficients by the RPM from Phantom 4 (with a high backscatter layer)

7.3.2. Backscatter Coefficients

The results of the simultaneously estimated backscatter coefficients for layers within the phantoms are presented in Figs. 7.6 and 7.7. These are compared with the established values for the phantom materials that were determined using test samples, as described in the Methods Section. Three different single element transducers were used to cover a broad frequency range for the test sample specimens, and hence three curves are shown for the lab data. Also shown are backscatter coefficients computed by the theory of Faran\textsuperscript{11} (see Section 2.2) using the properties of the glass spheres in the phantom, the number density of the spheres, and their size distribution.
Measured backscatter coefficients obtained with the LSM are in excellent agreement with results from lab methods, and both are in excellent agreement with the values predicted with Faran’s theory, though the agreement with the Faran computations was not as good at high frequencies. Such deviations between the measurements and predicted backscatter coefficients are sometimes found when a broad scatterer size distribution is used, but too few glass bead scatterer diameters are microscopically measured to adequately predict scattering. We have demonstrated that accurate BSC measurements can be made in phantoms with similar broad scatterer size distributions when the added effort is put forth. In this case that effort was deemed unnecessary for this work.

![Backscatter Coefficients](image)

**Figure 7.6.** Comparison of BSC measurement for Phantom 3
7.4 Discussion

Backscatter coefficient determinations for a ROI in tissue require corrections for attenuation losses over the beam path. A LSM enables these attenuation determinations for cases where the path is acoustically non-uniform. In this paper, an effective attenuation coefficient, defined as the total attenuation to the ROI divided by the total path length, is measured by applying the LSM to echo data derived from a clinical scanner equipped with a research interface. Comparisons are made with results obtained from a reference phantom method.

As expected, attenuation coefficients measured using the RPM are in good agreement with actual values when the test sample is uniform and the backscatter coefficient is constant.
throughout the sample (Phantom 2 results presented in Fig. 7.2). The RPM resulted in a smaller maximum percent error than the LSM. However, the LSM exhibited a lower variance for attenuation measurements within the region of interest, as demonstrated by its lower mean percent error.

Both the RPM and the LSM produced comparable results for Phantom 3, in which the backscatter coefficient is the same throughout but the attenuation coefficient along part of the path is significantly elevated (see Fig. 7.3). However, the RPM resulted in highest errors for Phantom 4, in which there was backscatter contrast along the beam path. In this case, the LSM yielded attenuation results that were within 16% of actual attenuation coefficients for the phantom.

For the non-uniform phantoms used here, the LSM provided more accurate attenuation and backscatter coefficients than the reference phantom technique. In particular, LSM results were less affected by backscatter variations along the beam propagation path than RPM results, as demonstrated in Fig. 7.4.

For most quantitative techniques, including the LSM, prior knowledge can be applied to help avoid solutions that are physically meaningless, or to enable more rapid solutions of the estimation problem. In the approach followed in this paper we assumed the backscatter coefficient over the ROI can be described by power law frequency dependence, \( b f^n \) where \( f \) is the frequency in MHz. The range of “allowable” values for \( n \) was left very broad. Still the least squares solution converged to the correct value, as demonstrated in Fig. 7.7. Upper bounds on the allowable attenuation coefficient that are beyond general values reported for most soft tissues
were applied (2dB/cm-MHz). Still, the LSM performed well for a phantom whose effective attenuation coefficient is significantly lower than this value. Though we used a broad range of attenuation coefficients and backscatter frequency dependency constraints to test the method, it is likely that for many problems these could be made narrower.

The assumption regarding the attenuation over the field not varying with respect to the transducer aperture appears to be valid for the phantom scanned here, even in the case of the layered phantoms shown in Fig.7.1. The extent that this assumption breaks down in more complex biological tissue will be the subject of future studies.

An advantage of the LSM method for assessments of acoustic properties within a ROI is that it only requires calculation of a power spectrum from the depth of interest. This may offer advantages for QUS studies applied to small tumors, for example. If the backscatter coefficients vs. frequency can be approximated as in Eq. (7-3), this method has a significant advantage when estimating backscatter coefficients without prior knowledge of the attenuation along the beam path, as is necessary for “conventional” methods.

One limitation of the LSM is that it assumes simple functional forms for attenuation and backscatter. If those assumptions are not well met, the measurements from this method may lose accuracy. One solution for this limitation might be applying a piece-wise continuous frequency range. This approach may help to describe the backscatter properties in more detail, and will be the subject of future investigations.
Another limitation is the assumption that the sample and reference have the same speed of sound. This algorithm is applied to the ratio of echo signal power spectra derived from a sample and from a reference phantom at the same depth. System and diffraction dependencies on the spectra are effectively eliminated when the ratio is taken, providing that the sample and the reference phantom have the same speed of sounds and when the assumed sound speed in the beam-former of an array system also matches the sound speeds in the media. We are investigating effects on attenuation measurements when there are speeds of sound mismatches among the sample, reference phantom, and beam-former as a next step.

7.5 Conclusion

The LSM described in this paper provides accurate measures of the total attenuation along the beam path as well as the backscatter coefficient vs. frequency in homogeneous as well as in 1-dimensional inhomogeneous phantoms.

7.6 References


Chapter 8:
Quantitative Ultrasound in *in vivo* Breast Masses

8.1 Introduction

The primary purpose of ultrasound breast imaging is to assess the nature of a breast abnormality. Breast ultrasound is usually used to augment the findings following diagnostic mammography. It is also sometimes used as a follow up to a physical exam by a physician or to a breast MRI study. It is also used in rare cases for breast cancer screening since mammograms are not suitable for all women (for example, 30yo high-risk women) and MRI may not be available to all women.

The American College of Radiology (ACR) Breast Imaging Reporting and Data System (US BI-RADS)\(^1\) has improved the assessment and management of breast masses by being predictive of benign and malignant disease. It also helps communication among healthcare providers, facilitates research, and provides better care for patients. However, many descriptors used in assessing the degree of abnormality of a mass are subjective and qualitative. For example, US BI-RADS includes descriptions of posterior acoustic features using the descriptors of “none,” “enhancement,” “shadowing,” and “combined pattern.” In addition, assessment of the echo pattern within the mass uses the descriptors “anechoic,” “hyperechoic,” “complex,” “hypoechoic,”
and “isoechoic.” This subjective and qualitative assessment process could cause inter-observer disagreement for some descriptors.

Quantitative ultrasound methods extract estimates of tissue characteristics that are expected to depend directly on acoustic wave-tissue interactions. This study investigated backscatter and attenuation coefficients which are closely related to the US BI-RADS descriptions of “echo pattern” and “posterior acoustic features”, respectively. Our hypothesis is that measured values of ultrasound attenuation and backscatter in breast masses will correlate with these US BI-RADS descriptors that are noted during (subjective) interpretations of ultrasound scans of the breast. This quantification should lead to better communication among health care providers. It might also lead to an improved description of masses.

This study also investigated ultrasound attenuation and backscatter as potential differential diagnostic markers. This chapter presents a comparison of local attenuation estimates from in vivo breast masses using two attenuation estimation methods. It also presents estimates of averaged backscatter coefficients (ABSCs) and effective scatterer diameters (ESDs) in breast masses. Finally, the estimated attenuation and ABSCs are correlated with the posterior acoustic features and echo pattern of US BI-RADS assessed by 3 observers.

8.2 Methods

8.2.1. Data collection

All human subject protocols were UW HSC-IRB approved and HIPAA compliant. Eighty-four patients who were scheduled for breast biopsy were recruited. The first 54 data sets were
collected using an elasticity/RF acquisition protocol, and 9 data sets that had good reference phantom data were selected from them. The next 30 data sets were collected using an RF acquisition protocol that employed beem steering, and 10 data sets were selected based on the biopsy results (including only fibroadenoma or carcinoma cases) and the mass size (larger than 7mm axially). Thus total of 19 data sets were included and among these were 11 fibroadenomas, 2 infiltrating ductal carcinomas, 2 invasive ductal carcinomas, 1 epithelial hyperplasia, 1 infiltrating lobular carcinoma, 1 invasive lobular carcinoma, and 1 adenocarcinoma. Reference phantom data were also obtained immediately after scanning the breast using the same transducer, transmit focus, and other equipment settings. The detailed data collection process and description of the reference phantom are presented in the Appendix (at the end of this chapter).

8.2.2. Comparison of attenuation coefficient estimates using the RPM with estimates using the Hybrid method

Data selection

This analysis included only the 9 data sets acquired under the elasticity/RF acquisition protocol (see Appendix).

Attenuation estimation

Two methods, the reference phantom method (RPM, see Section 2.1.1)\(^3\) and the hybrid method (see Section 2.1.3),\(^4\) were used to estimate the local attenuation within each of the 9 masses. Both methods apply the data from the reference phantom to account for system-dependent factors on echo data. The RPM algorithm first computes the ratio of the echo signal power spectrum from a location in the sample to that from a reference material, both spectra
obtained from the same depth. It then estimates an attenuation coefficient from the rate of change of the power spectra ratios with depth over a region of interest (ROI). The hybrid method normalizes the echo signal power spectrum from a windowed region of the sample to the power spectrum from a reference phantom. It then evaluates changes in the center frequency with depth.

A ROI in each breast mass was selected based on the B-mode image brightness uniformity within the tumor. The RPM assumes constant backscatter within the ROI, so a region judged to be reasonably homogeneous within the mass was chosen for analysis. The same ROI was used for the hybrid method. The ROI in the reference phantom matched that in the sample, but the ROI width included the center 3cm for all samples (for lower variance power spectral densities in the reference spectra). The echo signal power spectra in the mass and reference were calculated by applying a Chirp-Z transform (CZT)\(^5\) with a Hann window. The power spectrum analysis window size was 3mm (axially, 8 pulse lengths) by 3mm (laterally, 6 uncorrelated lines), and the overlap ratio was 90\%, both axially and laterally. The slope of the attenuation coefficient vs. frequency was estimated from the entire axial length of the ROI. The estimated slopes of attenuation coefficient vs. frequency within the ROI were averaged, and the attenuation estimates from all 7 frames were averaged to produce a single attenuation estimate for each mass. These data analysis procedures were identical for the RPM and hybrid method.

**8.2.3. Comparison of attenuation coefficients with the BI-RADS descriptor “posterior acoustic features”**

*Data selection*

The full set of data from all 19 subjects was used in this part of the study.
Attenuation estimation

The attenuation coefficient vs. frequency was estimated using the RPM for all 19 data sets. The attenuation values for the first 9 data sets were those obtained using the RPM for the method comparison study as described in Section 8.2.2. The ROI for each of the other 10 data sets was selected as the largest homogeneous region within the mass, based on the B-mode image. There were four data acquisitions for each mass in these data sets (two different planes each with two excitation frequencies). From these four data sets, the one with the largest ROI was chosen for this analysis. The RF echo signals from the zero degree steering angle were used. RF echo data from the reference phantom were acquired from 5 different frames (see Section 3.2.3), with the transducer translated in the elevation direction (perpendicular to the image plane) between frames.

The power spectrum analysis window size was 3-4mm (axially, 8-10 pulse lengths) by 3-4mm (laterally, 6-8 uncorrelated lines), depending on the mass size. The analysis windows were overlapped axially and laterally by 90% over the ROI. Power spectra in the sample and reference were calculated using Welch’s periodogram\(^6\) with a 2mm Hann window and the CZT\(^5\). The ratio of power spectra from the sample to that of the reference were calculated over the ROI and were used to estimate the slope of the attenuation coefficient vs. frequency using the entire axial length of the ROI. The attenuation estimates obtained over the ROI were averaged to obtain the final result.

Posterior acoustic features and attenuation coefficients
The posterior acoustic features shown in the B-mode image are related to the attenuation coefficient and size of the mass. Time-gain compensation (TGC) is commonly used to balance effects of ultrasound attenuation over depth, but TGC cannot compensate for lateral variations in attenuation. Thus, if a mass is more attenuating than the surroundings at the same depth, the tissue distal to the mass would appear darker in the B-mode image than tissue in surrounding tissues (assuming constant backscatter among the distal tissues). On the other hand, if the mass is less attenuating, the tissue distal to the mass would appear brighter than the surrounding tissue on a B-mode image.

To investigate the relationship between the BI-RADS’ posterior acoustic feature and estimated attenuation, the product of the attenuation coefficient and the antero-posterior (AP) dimension was calculated for each mass. The posterior echo feature of each mass was assessed, on a B-mode image generated from the RF echo data, by one radiologist and two physicists. The posterior echo features were evaluated by comparing the B-mode image brightness below the mass with the brightness of the adjacent tissue (at the same depth). In a subset of cases (data collected under steered beams/RF acquisition protocol), clinical B-mode images (employing spatial compounding, harmonic imaging, image enhancement, and multiple transmit foci) were acquired and assessed as well. Due to inter-observer variability, the final assessment of the posterior acoustic feature was determined based on the majority opinion from three observers. When there was no majority opinion, the posterior acoustic feature was rated as “competing interpretation.”

8.2.4. Backscatter coefficients and Echo pattern
Data selection

The backscatter coefficients (BSCs) were estimated from 17 of the 19 data sets described in Section 8.2.1. To compare (frequency-dependent) BSCs among masses, an overlapping frequency range among all data sets was determined. The backscattered echo signal bandwidths of one fibroadenoma and one epithelial hyperplasia did not overlap with those of the other data, and those two data sets were excluded.

Estimation of Backscatter coefficients

The BSCs were estimated using the reference phantom technique (see Section 2.3). To estimate the total attenuation through the inhomogeneous tissue path above the ROI, the least squares method (LSM; Chapter 7) was used. The power spectrum estimates described in Section 8.2.3 were used for BSC estimation. The constraints for the LSM (Eq. (7-9) in Chapter 7) were set as follows:

\[
10^{-7} \leq b_{s} \leq 10^{-1}, \quad 0 \leq n_{s} \leq 5, \quad 0.2 \leq \alpha_{s}(dB/cm-MHz) \leq 2
\]  

(8-1)

The LSM was used to estimate the effective attenuation coefficient and the depth of the ROI and from these the accumulated attenuation over the path above the ROI was accounted for. The BSC as a function of frequency was estimated by multiplying the ratio of the attenuation-corrected power spectrum from the sample to that of the reference, with the BSC function of the reference. The estimated BSCs within the ROI were averaged spatially to obtain the final result.

Echo pattern and backscatter coefficients
The echo pattern within the mass is related to its backscatter. To compare the backscatter among the masses, the BSCs were averaged (ABSCs)\textsuperscript{7,8} within the overlapping frequency range (5-8MHz) for all 17 cases. The echo pattern of each mass was evaluated with the B-mode image generated from the RF echo signals by comparing the echo level within the mass with the echo level of fat. The clinical B-mode images were also assessed when available (see Section 8.2.3). Just as with the attenuation and posterior feature data, the final determination of the echo pattern was based on the majority opinion. When there was no majority opinion, the echo pattern of mass was rated as “competing interpretation.” The echo pattern of each mass was also compared with its ABSC results.

8.2.5. Effective scatterer diameter estimation

The ESD was estimated from the BSCs over the overlapping frequency range (5-8MHz) using a Gaussian form factor (Section 2.4). The ESDs for all 17 cases were computed (Eq. (2-21) in Chapter 2) from the estimated BSCs described in Section 8.2.4.

8.3 Results

*Comparison of attenuation coefficient estimates using the RPM with those from the hybrid method*

Attenuation estimates for the first group of 9 masses are listed in Table 8.1. Inspection of the data in Columns 3 and 4 indicate the two methods applied in this study provided comparable results. The difference in the estimates using the hybrid method and the RPM ranged from 1.6-39.2%. The maximum difference occurred for patient 7 (epithelial hyperplasia), and the minimum difference occurred for patient 2 (fibroadenoma).
To assess the attenuation variability among different types of masses, the attenuation estimates from the 6 fibroadenomas were averaged. The mean for the fibroadenomas are shown along with the attenuation values of the other mass types in Fig. 8.1. The error bars indicate one standard deviation. A red color bar indicates results from the RPM and a pink bar represents results from the hybrid method. The results using the two methods were consistent (except for the epithelial hyperplasia). The attenuation value of the invasive ductal carcinoma was higher than the mean attenuation value of the fibroadenomas, and the attenuation value of the infiltrating lobular carcinoma was lower than that of the fibroadenomas. The values for both carcinoma types fell within the range found for fibroadenomas.

Table 8.1. Estimated slopes of the attenuation coefficient vs. frequency from 9 masses using the RPM and hybrid method.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Biopsy result</th>
<th>RPM result (dB/cm-MHz)</th>
<th>Hybrid result (dB/cm-MHz)</th>
<th>% difference in estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>fibroadenoma</td>
<td>1.83</td>
<td>1.61</td>
<td>12.0</td>
</tr>
<tr>
<td>2</td>
<td>fibroadenoma</td>
<td>1.26</td>
<td>1.28</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>fibroadenoma</td>
<td>1.08</td>
<td>0.88</td>
<td>18.5</td>
</tr>
<tr>
<td>4</td>
<td>fibroadenoma</td>
<td>1.05</td>
<td>0.89</td>
<td>15.2</td>
</tr>
<tr>
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<td>fibroadenoma</td>
<td>1.35</td>
<td>1.68</td>
<td>24.4</td>
</tr>
<tr>
<td>6</td>
<td>fibroadenoma</td>
<td>1.08</td>
<td>1.19</td>
<td>10.2</td>
</tr>
<tr>
<td>7</td>
<td>epithelial hyperplasia</td>
<td>1.25</td>
<td>0.76</td>
<td>39.2</td>
</tr>
<tr>
<td>8</td>
<td>invasive ductal carcinoma</td>
<td>1.88</td>
<td>1.84</td>
<td>2.1</td>
</tr>
<tr>
<td>9</td>
<td>infiltrating lobular carcinoma</td>
<td>0.81</td>
<td>0.89</td>
<td>9.9</td>
</tr>
</tbody>
</table>
Figure 8.1. Slopes of the attenuation coefficient vs. frequency estimated using the RPM and hybrid method.

**Attenuation coefficients and posterior acoustic features**

The slopes of the attenuation coefficient vs. frequency estimated from all 19 masses using the RPM are presented in Table 8.2 (column 5). The patient number was rearranged based on the pathology results so that the attenuation variation among different mass types can be easily noted. The AP dimension (column 6) and the posterior acoustic features (columns 3 and 4) are also presented in Table 8.2. The product of the attenuation value and AP dimension was computed for each mass. This is plotted with its corresponding posterior acoustic feature in Fig. 8.2. In Fig. 8.2(a) the posterior acoustic feature was determined from the assessment on B-mode images.
from the RF echo data. In Fig. 8.2(b) the posterior acoustic feature was obtained from the assessment on clinical B-mode images for the 10 data sets obtained under steered beams/RF acquisition protocol while the acoustic feature of the other data set was the same as that in Fig. 8.2(a). The red dashed line was drawn on the approximate boundary separating the descriptor “shadowing” from other posterior acoustic features. Based on the red dashed line in Fig. 8.2, the posterior acoustic feature of “shadowing” corresponds well with the relatively high total attenuation values. Attenuation values alone did not differentiate tumors types in this study, and it shouldn’t be expected to given the prevalence of a clinical finding of “shadowing” and fraction with that finding that are cancers.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Biopsy result</th>
<th>Posterior acoustic feature (Lab B-mode)</th>
<th>Posterior acoustic feature (Clinical B-mode)</th>
<th>RPM result (dB/cm-MHz)</th>
<th>AP dimension (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>fibroadenoma</td>
<td>None</td>
<td>N/A</td>
<td>1.83</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>fibroadenoma</td>
<td>None</td>
<td>N/A</td>
<td>1.26</td>
<td>0.9</td>
</tr>
<tr>
<td>3</td>
<td>fibroadenoma</td>
<td>Enhancement</td>
<td>N/A</td>
<td>1.08</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>fibroadenoma</td>
<td>Combined</td>
<td>N/A</td>
<td>1.05</td>
<td>1.4</td>
</tr>
<tr>
<td>5</td>
<td>fibroadenoma</td>
<td>None</td>
<td>N/A</td>
<td>1.35</td>
<td>1.2</td>
</tr>
<tr>
<td>6</td>
<td>fibroadenoma</td>
<td>Enhancement</td>
<td>N/A</td>
<td>1.08</td>
<td>0.8</td>
</tr>
<tr>
<td>7</td>
<td>fibroadenoma</td>
<td>Competing interpretation</td>
<td>Enhancement</td>
<td>1.53</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Table 8.2. Estimated slopes of attenuation coefficient vs. frequency by the RPM, AP dimension, and posterior acoustic feature for 19 breast masses.
<table>
<thead>
<tr>
<th>Patient number</th>
<th>Biopsy result</th>
<th>Posterior acoustic feature (Lab B-mode)</th>
<th>Posterior acoustic feature (Clinical B-mode)</th>
<th>RPM result (dB/cm-MHz)</th>
<th>AP dimension (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>fibroadenoma</td>
<td>Competing interpretation</td>
<td>None</td>
<td>1.00</td>
<td>0.8</td>
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<td>fibroadenoma</td>
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<td>Enhancement</td>
<td>0.42</td>
<td>1.2</td>
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<tr>
<td>10</td>
<td>fibroadenoma</td>
<td>Shadowing</td>
<td>Shadowing</td>
<td>2.09</td>
<td>1.7</td>
</tr>
<tr>
<td>11</td>
<td>fibroadenoma</td>
<td>Enhancement</td>
<td>Enhancement</td>
<td>0.63</td>
<td>1.4</td>
</tr>
<tr>
<td>12</td>
<td>epithelial hyperplasia</td>
<td>Shadowing</td>
<td>N/A</td>
<td>1.25</td>
<td>1.5</td>
</tr>
<tr>
<td>13</td>
<td>infiltrating lobular carcinoma</td>
<td>Combined</td>
<td>N/A</td>
<td>0.81</td>
<td>1.8</td>
</tr>
<tr>
<td>14</td>
<td>infiltrating ductal carcinoma</td>
<td>None</td>
<td>Enhancement</td>
<td>1.80</td>
<td>0.8</td>
</tr>
<tr>
<td>15</td>
<td>infiltrating ductal carcinoma</td>
<td>Competing interpretation</td>
<td>None</td>
<td>0.92</td>
<td>1.3</td>
</tr>
<tr>
<td>16</td>
<td>invasive ductal carcinoma</td>
<td>None</td>
<td>N/A</td>
<td>1.88</td>
<td>1.1</td>
</tr>
<tr>
<td>17</td>
<td>invasive ductal carcinoma</td>
<td>Combined</td>
<td>Shadowing</td>
<td>1.52</td>
<td>1.8</td>
</tr>
<tr>
<td>18</td>
<td>adenocarcinoma</td>
<td>None</td>
<td>Enhancement</td>
<td>1.30</td>
<td>0.7</td>
</tr>
<tr>
<td>19</td>
<td>invasive lobular carcinoma</td>
<td>Shadowing</td>
<td>Shadowing</td>
<td>1.80</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Figure 8.2. Total attenuation (product of the slope of the attenuation coefficient vs. frequency and AP dimension) in each mass and its posterior acoustic feature. The red dashed line is drawn on the approximate boundary of “shadowing” and other acoustic features; (a) with lab B-mode image, (b) with clinical B-mode image for subset of data.
**Backscatter coefficients and BI-RADS “echo pattern”**

The BSCs were averaged over 5-8MHz for each mass. The resultant “average backscatter coefficients” (ABSCs) are presented with corresponding echo patterns of masses in Fig. 8.3. In Fig. 8.3(a), the echo pattern was determined from the assessment on the B-mode images generated from RF echo data. In Fig. 8.3(b), the echo pattern was determined from the 10 sets of data obtained under the steered beams/RF acquisition protocol with clinical B-mode images while the echo patterns of the other 7 data set were the same as those in Fig. 8.3(a). No strong statements can be made about the utility of the echo pattern for lesion differentiation, or correlation of echo pattern findings with ABSC values since nearly all tumors in this data set had “hypo-echoic” findings. However, most tumors with ABSC values below 0.01cm\(^{-1}\)sr\(^{-1}\) had “hypo-echoic” findings.
Averaged backscatter coefficients vs. attenuation coefficient

The ABSCs vs. attenuation coefficients (slope of attenuation coefficient vs. frequency) are plotted in Fig. 8.4 (similar to the plots by D’Astous et al.⁹). The red dashed line in Fig. 8.4 is drawn on the approximate boundary of fibroadenomas and carcinomas. Notice in this plot, the majority of fibroadenomas are to the left of the boundary, while all malignant cancers are to the right.
Figure 8.4. Averaged BSC vs. attenuation coefficient (slope of attenuation coefficient vs. frequency) is plotted for each mass. The red dashed line is drawn on the approximate boundary between fibroadenomas and carcinomas.

Effective scatterer diameter estimation

The estimated ESDs over the ROI from 5-8MHz using a Gaussian form factor were averaged for each breast mass. The mean and standard deviation of the ESD estimates are presented in Fig. 8.5. Though the mean ESD size alone did not differentiate the mass type, most of the fibroadenomas had more variation in ESD within the ROI than the carcinomas had in this study. The red dashed line in Fig. 8.5 is drawn on the approximate boundary of fibroadenomas and carcinomas.
Figure 8.5. ESDs (calculated from 5-8MHz) over the ROI were averaged and the mean and standard deviation are plotted for each mass.

8.4 Discussion

Comparison of attenuation coefficient estimates

The slopes of attenuation coefficient vs. frequency estimated by the RPM and hybrid method were consistent, except for the case of epithelial hyperplasia as shown in Fig. 8.1. The possible cause of the estimate difference in epithelial hyperplasia is the size of the mass. The epithelial hyperplasia had the smallest ROI among the 9 masses, and the power spectrum was estimated using a relatively small number of beamlines. In addition, the distance used to estimate the change of power spectra ratios with depth was shortest. Therefore, the attenuation estimates for this case likely have the highest uncertainty.
The consistency of attenuation estimates is encouraging. The results motivate continued investigation into quantitative in vivo breast mass attenuation estimation since there is a lack of data in the literature for specific masses.

*Attenuation coefficients and posterior acoustic features*

Based on Fig. 8.2, high total attenuation in the mass corresponded to the posterior acoustic feature of “shadowing,” while low total attenuation corresponded to “none” and “enhancement.” Although the attenuation values for the tumors characterized as having posterior acoustic features of “none” and “enhancement” were not significantly different (provide mean and STD based on data in figure 8.2a), the total attenuation values corresponding to the posterior acoustic feature “none” were somewhat higher than those corresponding to “enhancement”. We believe further refinement in attenuation estimations is worth pursuing in order to continue to study this property.

This study demonstrated inter-observer variability for the assessment of the posterior acoustic echo feature, as well as an inter-image variability for this descriptor. This may have been caused by the qualitative evaluation of this feature. One component of inter-image variability might be due to differences between operating settings under which the two image types were acquired. In most cases, the lab B-mode images showed less contrast and a more poorly defined lesion boundary than the B-mode images derived by the scanner software. This could have contributed to the assessment of “competing interpretation” in Fig. 8.2(a). Finally the choice of the ROI for attenuation estimation could have contributed to the discrepancy between the QUS results and the BI-RADS assessment. However, the correlation between the total
attenuation and the posterior echo feature shown in Fig. 8.2 demonstrated the potential to quantify the attenuation in the mass.

In the future, we will continue to quantify the attenuation within masses, not only to correlate with the posterior echo features, but to investigate the attenuation coefficient as a diagnostic marker. In addition, compounding breast data acquired from angles other than 0° will be considered, since compounding helps to reduce the variance of attenuation estimates.\textsuperscript{10}

\textit{Backscatter coefficients and the BI-RADS “echo pattern”}

Most masses with relatively low ABSCs (below 0.01\,cm\textsuperscript{-1}\,sr\textsuperscript{-1}) were characterized with the echo pattern of “hypo-echoic”. Since few tumors were characterized with the echo pattern of “iso-echoic,” no strong statements about correlations based on the ABSC value can be made. The differences in tumor characterization in Figs. 8.3(a) and 8.3(b) might be explained as described above (see \textit{Attenuation coefficients and posterior acoustic features}). The inter-observer variability was higher in the results for Fig. 8.3(a) than those for Fig. 8.3(b). The black dashed circle included the carcinomas with relatively low ABSCs. This might provide additional information relative to the properties of the carcinomas for future studies.

The study by Hong \textit{et al.}\textsuperscript{11} showed that among 403 masses, the echo patterns of “iso-echoic” and “hypo-echoic” had 12\% prevalence and 80\% prevalence, respectively. Thus, most breast masses viewed on clinical ultrasound scans are characterized with one of these two descriptions, and thus, it is hard to classify the masses based on the echo pattern. On the other hand, the results in Fig. 8.3 suggest that characterizing the tumors with an absolute quantity
might improve differentiation (although some cancers have relatively high ABSC, most are quite low compared to benign tumors).

**Averaged backscatter coefficient vs. attenuation coefficient**

In Fig. 8.4, the red dashed line shows the combination of backscatter and attenuation values has the potential to aid in differentiation of benign and malignant masses, though there were two fibroadenomas in the “carcinoma” side of the red line. Fibroadenomas had relatively higher ABSC values and lower attenuation coefficients than carcinomas. We will extend this study by collecting and analyzing more breast data.

**Effective scatterer diameter estimation**

The BSC is a function of frequency; the overall magnitudes of BSCs among masses were evaluated by computing the ABSC values above. The ESD was calculated to assess the variability of the frequency dependence of BSCs among masses. We applied a Gaussian form factor in the mean scatter size estimation. As seen in Fig. 8.5, the mean and standard deviations of ESD estimates fell into a narrow range of values for our patient data. However, the pair of parameters showed potential to separate most fibroadenomas from carcinomas. It should be noted that the bandwidth used for effective scatterer diameter estimation (5-8MHz) was quite narrow and thus the estimated ESD sizes likely have relatively high uncertainty. Relatively broadband data are needed for accurate ESD estimation (refer Section 2.4). In the future, the comparison of ESD estimates using all available bandwidths may be tried.

**General Comment**
One of limitations in this study was a possible sound speed mismatch between reference phantoms and tissues during data collection. The sound speed of the reference phantom was 1490m/s. To match the sound speeds of reference phantom and breast tissue as closely as possible within the allowable sound speed settings of the clinical scanner, the sound speed in the beamformer (refer Chapter 9) was set as 1450m/s. In the RF data analysis, the conventional 1540m/s was assumed since the sound speed within breast masses has not been determined. To minimize the sound speed mismatch effect reported in Chapter 9, the recent data were collected with setting a transmit focus distal to the lesion being scanned. However, further effort to match all sound speeds will be needed in the future to reduce any possible error in estimation of QUS parameters.

8.5 Conclusion

The attenuation coefficients estimated from the RPM and hybrid method were consistent, except for one relatively small tumor, and demonstrated that the attenuation within the breast mass can be quantified. The product of the slope of the attenuation coefficient vs. frequency and AP dimension was used to compute the total attenuation in the mass. The resultant value showed potential to provide a quantitative measure for the BI-RADS “posterior acoustic echo feature”. The ABSC values were well correlated with the subjectively determined “echogenicity” within breast masses. The combination of the ABSC and attenuation coefficient showed potential to differentiate fibroadenomas and carcinomas in this study. Finally, most of the fibroadenomas exhibited relatively high standard deviations of ESD estimates within the mass compared to that from the carcinomas though there were a few exceptions.
8.6 References


Appendix

1. Data collection

Elasticity/RF acquisition protocol

Fifty-four patients who were scheduled for breast biopsy were recruited for an elasticity/RF acquisition study. These patients were scanned at the University of Wisconsin Hospitals and Clinics Breast Center (Madison, WI, USA) using a Siemens Antares (Siemens Medical Solutions USA, Inc., Malvern, PA) equipped with a VFX13-5 linear array transducer operated at a center frequency of 10MHz. Because data were acquired during elasticity imaging experiments, “elasticity imaging” mode was used to collect the patient data. Using the same system setting as for the breast scanning, a reference phantom with known acoustic properties was scanned after each patient scan. From this group of 54 patients, we selected 9 data sets that had good reference phantom data. This group included 6 fibroadenomas and one each of invasive ductal carcinoma, infiltrating lobular carcinoma, and epithelial hyperplasia. Since the elasticity mode needs a small amount of mechanical strain to image the object, the RF breast data recorded during the elasticity mode have small deformations from one frame to the next. Each frame consisted of either 256 or 312 acoustic scan lines per image frame. For this investigation, 7 consecutive frames with minimal overall deformation were chosen for each set of patient data.

Steered beams/RF acquisition protocol

The next thirty patients who were scheduled for breast core biopsy were scanned with a Siemens S2000 (Siemens Medical Solutions USA, Inc., Malvern, PA) using an 18L6 linear array transducer operated at center frequencies of 15MHz and 7MHz. Using the Axius Direct
ultrasound research interface (URI)\textsuperscript{A2}, we obtained RF echo data from the longitudinal and transverse planes of the mass. This was done using ultrasound beams steered from -20° to +20°, in 5° increments, at each center frequency. The reference phantom scanning was performed using the same system settings. Based on the biopsy results (including only fibroadenoma or carcinoma cases) and the mass size (larger than 7mm axially), we selected 10 data sets. This group included 5 fibroadenomas, 2 infiltrating ductal carcinoma, and one each of invasive ductal carcinoma, invasive lobular carcinoma, and adenocarcinoma.

Reference phantom

The reference phantom used for the elasticity/RF acquisition (first 54 patient data) was made with 6.4g of 3-45µm-diameter glass spheres uniformly distributed in a 1600cc gel background. The background material was an emulsion containing 70% safflower oil.\textsuperscript{4} The top of the reference phantom was covered with a plastic-coated aluminum foil (made by Gammex Inc., Middleton, WI, USA). The acoustic properties of the reference phantom were estimated on test samples manufactured at the same time as the reference phantom, applying a narrow-band substitution method.\textsuperscript{A3} The sound speed turned out to be 1492m/s at 2.5MHz. The measured attenuation coefficients from 2-10MHz were fit to a line to estimate the slope of the attenuation coefficient vs. frequency which was to be 0.54dB/MHz-cm.

The reference phantom used for the steered beams/RF acquisition protocol had the same composition as the phantom used for the elasticity/RF acquisition; however, the top of this phantom was covered with a 25µm-thick Saran\textsuperscript{TM} wrap (Dow Chemical, Midland MI, USA) rather than plastic-coated aluminum foil (to simplify thin layer transmission calculations with
steered beams). The acoustic properties of the reference phantom were estimated using a narrow-band substitution method\textsuperscript{44} on test samples manufactured at the same time as the reference phantom. The sound speed was 1492m/s at 2.5MHz. Measured attenuation coefficients at frequencies from 2-10MHz were fit to a power law function of frequency, yielding $\alpha(f)$ (dB/cm) = $0.256 f^{1.366}$, where $f$ is the frequency in MHz.

2. References


Chapter 9:
Ultrasound Attenuation Measurements using a Reference Phantom with a Sound Speed Mismatch

This chapter is published as:
Nam, K.; Rosado-Mendez, I.M.; Rubert, N.C.; Madsen, E.L.; Zagzebski, J.A.; Hall, T.J., Effects of Sound Speed Mismatch on Ultrasound Attenuation Measurements using a Reference Phantom. Ultrasonic Imaging, 33, 251-263

9.1 Introduction

Quantitative ultrasound has been introduced to supplement qualitative evaluations of acoustic properties that are done during clinical interpretation of ultrasound scans. For example, attenuation levels of tissues are judged qualitatively on B-mode images by their degree of shadowing or on the basis of penetration depth. When measured quantitatively, attenuation has shown potential to characterize the degree of diffuse disease and remove some of the subjectivity when describing focal lesions. Measurements of ultrasound attenuation have been used to differentiate fatty liver from normal liver\(^1,2,3\) and benign tumors from malignant ones\(^4\) in the liver. Other researchers have suggested that ultrasound attenuation has diagnostic value in bone disease,\(^5,6\) in predicting the condition of the cervix during pregnancy,\(^7\) and in differential diagnosis of breast masses.\(^8,9\) Attenuation values have also been utilized to detect and characterize thermal lesions in ablation therapy.\(^10\)
As demonstrated in this thesis and shown by previous investigators, attenuation can be estimated from echo data derived from clinical ultrasound systems that provide unprocessed, radiofrequency (RF) echo signals.\textsuperscript{11,12} To do so, we also have shown previously that system dependent factors affecting the echo signal, such as frequency dependent sensitivity of the transducer-pulser-receiver system and beam focusing patterns must be accounted for. Use of the reference phantom technique introduced in Chapter 2 is a straightforward way to eliminate these system dependent factors. With the reference phantom method\textsuperscript{13} (RPM, see Section 2.1.1), one computes the ratio of echo signal power spectra from the tissue to power spectra derived at the same depth from a well-characterized reference medium. The slope of the power spectra ratio as a function of depth yields the attenuation coefficient of the tissue. The RPM provides accurate attenuation values over homogeneous tissue regions,\textsuperscript{14} and it has been utilized successfully to measure attenuation in human liver with fatty infiltration or with cirrhosis,\textsuperscript{15,16} to monitor changes in canine livers resulting from glucocorticoid administration\textsuperscript{16} and to assess changes in the cervix during cervical ripening.\textsuperscript{7}

Accounting for diffraction effects on the echo signal with the RPM requires that the speed of sound in the reference media ($c_{\text{ref}}$), must be approximately the same as that of the sample ($c_{\text{sam}}$).\textsuperscript{13} Exact guidelines for how close the sound speeds need to be were not presented by Yao.\textsuperscript{13} However, Tu\textsuperscript{17} reported that a difference in speeds of sound of 2.1% resulted in substantial artifacts on attenuation coefficient images computed using the RPM with an array transducer. Chen\textsuperscript{18} studied degradation of resolution in phantoms whose sound speeds differed from that used in the beamformer ($c_{\text{bf}}$) of an array system. Although Chen directed his work towards spatial resolution considerations, his simulations point to mismatches in focal patterns
when transmitting into media having different sound speeds, and the mismatches could lead to artifacts when applying the RPM for determining attenuation. Omari et al.\textsuperscript{19} report that a hybrid technique\textsuperscript{20} (see Section 2.1.3) for estimating attenuation, normalizing the echo signal power spectra from a region of interest (ROI) to the power spectrum from a reference phantom and then evaluating changes in the center frequency with depth, may be less prone to errors than the RPM when there are sound speed differences between the tissue and reference media. Omari et al.\textsuperscript{19} did not study depth dependencies of attenuation estimates, one of the problems vividly brought out by Tu’s\textsuperscript{17} work.

The goal of the work described in this chapter was to investigate effects of sound speed mismatches on attenuation estimates done using the RPM. Emphasis is given to results at different distances from the transducer as well as with different transmit focal depths. The work is applied to array transducers with electronic beamforming. We evaluate results for tissue-mimicking phantoms in which the speed of sound is both lower and higher than that of the reference phantom. Possible improvements in estimation accuracy are considered for cases in which the sound speed used in the system beamformer matches that of the media scanned and where steps are taken to precisely match depths in the reference and sample from which power spectra are computed and compared. Both experimental and simulation results are presented.

9.2 Methods

9.2.1. Experimental phantoms
Three tissue-mimicking homogeneous phantoms, each having a different sound speed, were utilized. The phantoms consist of 15cm x 5cm x 15cm water-based agarose gel media housed in rectangular 9mm thick acrylic boxes. One 5cm x 15cm surface on each phantom is bounded with a 25µm thick Saran-Wrap® (Dow Chemical, Midland MI, USA) scanning window. The phantoms were made with 5-43µm diameter glass bead scatterers spatially randomly distributed in the gel, at a concentration of about 400 beads/mm³. In constructing the phantoms, molten agar was prepared by mixing dry agarose powder into an n-propanol water mixture, where the n-propanol concentration was chosen to provide sound speed values of approximately 1500m/s, 1540m/s, and 1580m/s in the different phantoms. Graphite powder (32g/liter) was added to the molten gel to provide approximately 0.5dB/cm-MHz ultrasound attenuation in each phantom. Phantoms were rotated at 1rpm during congealing to prevent gravitational settling of particles.

The acoustic properties of the phantoms were measured using 2.5cm thick, 7.6cm diameter test samples produced at the time of construction of each phantom. Four pairs of unfocused single element transducers were used to span the 2.5-10MHz frequency range, and a narrowband substitution method²¹ was applied for both attenuation and sound speed measurements. Sound speed values were determined only at 2.5MHz since dispersion (over the analysis frequency range) is negligible in these materials. Attenuation coefficients were fit to a power law of the form \( \alpha(f) = \alpha_o f^n \) where \( \alpha_o \) and \( n \) are constants; resulting values for \( \alpha_o \) and \( n \) are shown in Table 9.1. Measured speeds of sound also are presented in Table 9.1. The slope of attenuation coefficient vs. frequency are shown at 5MHz, the approximate center frequency of
echo signal power spectra obtained over the ROIs in the samples and reference phantom when they are scanned with clinical ultrasound equipment used in these studies.

Table 9.1. Sound speed and attenuation measurements of three phantoms

<table>
<thead>
<tr>
<th></th>
<th>1500m/s Phantom</th>
<th>1540m/s Phantom</th>
<th>1580m/s Phantom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sound speed</td>
<td>1499m/s</td>
<td>1539m/s</td>
<td>1581m/s</td>
</tr>
<tr>
<td>$\alpha_o$</td>
<td>0.433dB/cm</td>
<td>0.491dB/cm</td>
<td>0.524dB/cm</td>
</tr>
<tr>
<td>$n$</td>
<td>1.179</td>
<td>1.114</td>
<td>1.085</td>
</tr>
<tr>
<td>Slope of Attenuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coefficient vs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency at 5MHz</td>
<td>0.559dB/cm-MHz</td>
<td>0.573dB/cm-MHz</td>
<td>0.591dB/cm-MHz</td>
</tr>
</tbody>
</table>

9.2.2. Clinical scanner data collection

RF echo data were collected using a Siemens Acuson S2000 system (Siemens Medical Solutions USA, Inc., Malvern, PA) with a 9L4, 192 element linear array transducer driven at a center frequency of 6MHz. The Axius Direct ultrasound research interface on the system was used to acquire frames of RF data at a 40MHz sampling frequency.\textsuperscript{12} Each frame consisted of signals from 456 acoustic beam lines. Ten frames were acquired from each phantom, each representing data from an 8.5cm (axial) by 3.8cm (lateral) field of view, with an elevational translation or a rotation of the transducer between each frame to obtain statistically independent echo data from one frame to the next. However the scan windows of the phantoms were quite narrow (5cm) so the ten frames of RF data recorded during each experiment may have been partially correlated. The same control settings, including time-gain compensation, overall gain, and transmit focal distance were used for each phantom. Separate experiments were done with
transmit focal distances of 2cm, 3cm, 4cm, 5cm, and 7cm, in each experiment recording both sample and reference phantom data using the same control settings. The research interface allowed the sound speed assumed in the beamformer to be varied from the default value of 1540m/s. Data from the 1500m/s and 1580m/s phantoms were recorded setting the beamformer sound speed either at 1540m/s or equal to the sound speed of the scanned phantom.

For comparison, the experimental conditions were simulated using a frequency domain B-mode imaging model developed in our laboratory. The computational model assumes a spatially random distribution of scatterers within a medium of specified attenuation coefficient and sound speed. The program incorporates transmit focusing and dynamic receive beamforming with any desired sound speed. Three homogeneous numerical phantoms with attenuation coefficients and sound speeds matching those of the physical phantoms were simulated. Each numerical phantom contained scatterers at a concentration of 10 scatterers/mm$^3$ and each of these simulated phantoms had a backscatter coefficient equal to $2 \times 10^{-6} f^3 \text{ cm}^{-1} \text{sr}^{-1}$, where $f$ is the frequency in MHz. The numerical phantoms were 8cm (axial) by 4cm (lateral) by 1cm (elevational). Sound speeds of the numerical phantoms were set to 1500m/s, 1540m/s, and 1580m/s, which were within one standard deviation of measured values of sound speeds of the physical phantoms.

To enable close comparison with experiment, the measured attenuation values at 5MHz shown in Table 9.1 were applied to the simulated phantoms. The simulated transducer mimicked a Siemens 9L4 linear array transducer. This probe has 192 elements whose sizes are 0.18mm (lateral) by 10mm (elevational) with a center to center spacing of 0.2mm. Using the simulated
phantoms, a single frame of RF echo data for 200 closely spaced acoustic beam lines was generated over the 8cm by 4cm region that was simulated. The aperture of the transducer was adjusted to keep a constant F-number of 2 during dynamic receiving focusing. While the clinical array transducer in the experiment has a mechanical lens providing a fixed elevational focus, the simulated transducer did not use elevational focusing. A Gaussian-shaped pulse with a center frequency of 6MHz and a 70% bandwidth was assumed in the model.

9.2.3. Four data acquisition and analysis cases

Experimentally, the 1500m/s and the 1580m/s phantoms were used as “samples” while the 1540m/s phantom served as the reference. RPM attenuation estimations were studied for four conditions, or cases as described in Table 9.2.

<table>
<thead>
<tr>
<th>Case</th>
<th>Beamformer sound speed, $c_{bf}$</th>
<th>Depth calculation sound speed, $c_z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case I</td>
<td>1540m/s</td>
<td>1540m/s</td>
</tr>
<tr>
<td>Case II</td>
<td>1540m/s</td>
<td>Uses each phantom’s sound speed</td>
</tr>
<tr>
<td>Case III</td>
<td>Match to each phantom’s sound speed</td>
<td>1540m/s</td>
</tr>
<tr>
<td>Case IV</td>
<td>Match to each phantom’s sound speed</td>
<td>Uses each phantom’s sound speed</td>
</tr>
</tbody>
</table>

9.2.4. Attenuation estimation

The attenuation was estimated using the RPM (see Section 2.1.1). A ROI extending from 1-6cm axially and 1-3cm in width was selected from the simulated data. The near field data from the experiment suffered from ring-down and other artifacts associated with the transducer-
to-phantom surface, so the ROI in the experimental data was made 0.5cm shorter than the ROI used in simulations. Except for this minor adjustment, both experimental and simulated results are from overlapping regions.

Power spectra in the sample and reference were calculated using Welch’s method.\textsuperscript{23} In this method, a segment of data spanning a depth of 4mm (5.19\(\mu\)s duration using 1540m/s) was divided into sub-segments (2mm) with 75\% overlap. A Hann gating window was applied to each sub-window computing the Chirp-Z transform,\textsuperscript{24} and the power spectrum is obtained by the averaging the power spectra from sub-segments. The same process was applied to several beamlines (4mm-wide, 48 acoustic scan lines for experimental data, and 40 scan lines for simulated data). The echo signal power spectrum over the specific “analysis window (4mm by 4mm)” was obtained by averaging the power spectra from the beamlines within the analysis window. This process is repeated on multiple, overlapping data segments over the entire ROI. Analysis windows were allowed to overlap by 75\% both axially and laterally. The ratios of the power spectra from the sample to those of the reference phantom at the same depth were grouped in 8mm segments in the axial direction, and the logarithm of the ratios were fit to a straight line using a least-squares fitting routine. The slope of this line was used to estimate the attenuation coefficient (neper/cm) as shown in Eq. (2-4) in Chapter 2. This was done over the frequency range of 5-6MHz and 4-8MHz for experimental data and simulations, respectively. The frequency range used for the experimental data was limited to the 5-6MHz bandwidth to minimize any errors that would be caused by the slightly nonlinear frequency dependent attenuation in the phantoms, noted in Table 9.1. However, the range used for the simulated data, where attenuation was modeled as being proportional to frequency, was 4-8MHz to enable a
greater number of independent estimates of the slope of attenuation coefficient vs. frequency. The slopes of attenuation coefficient vs. frequency were obtained by converting to dB/cm and then dividing by the frequency in MHz. The slopes of attenuation coefficient vs. frequency were obtained over the entire depth from which data were acquired.

Attenuation values were obtained with the transmit focus at 2cm, 3cm, 4cm, 5cm, and 7cm for both sample phantoms. Attenuation estimates from the same depth were averaged laterally over the ROI.

Biases of RPM results with respect to the laboratory measurements were quantified using an absolute percent error, defined as:

\[
\text{Absolute percent error}(z) = \left| \frac{\alpha_{\text{estimated}}(z) - \alpha_{\text{known}}(z)}{\alpha_{\text{known}}(z)} \right| \times 100, \tag{9-1}
\]

where \(\alpha_{\text{estimated}}(z)\) and \(\alpha_{\text{known}}(z)\) are the estimated attenuation coefficients using the RPM and the laboratory measurements, respectively.

### 9.3 Results

Attenuation coefficient slopes vs. depth obtained from simulated and experimental data with the transmit focus at 2cm are presented in Fig. 9.1 for the 1500m/s phantom and in Fig. 9.2
for the 1580 m/s phantom. The horizontal line in each plot indicates the expected slope of attenuation coefficient vs. frequency at 5 MHz based on through transmission measurements made on test samples. As can be seen in Fig. 9.1, without accounting for differences in speeds of sound in the sample, beam former, and reference (Case I) significant deviations from the expected attenuation values are found, particularly near the 2 cm transmit focus applied in the simulation program for these data. This bias is reduced somewhat with partial corrections, either by precisely matching the depths from which echo signal power spectra for the sample and reference are computed (Case II) or by applying a beam former sound speed that accurately matched the sound speed of the sample or the reference media when data were acquired (Case III). The smallest deviations between results from simulated echo data and expected values are observed in Case IV, where both corrections schemes are applied.

![Figure 9.1](image.png)

**Figure 9.1.** Slopes of attenuation coefficient vs. frequency over the ROI with a 2 cm transmit focal distance, for all four experimental cases (Cases I, II, III, IV) shown on each graph. Subplot (a) is from simulated data while subplot (b) shows results from experiments. The sound speed in the sample is 1500 m/s and that in the reference phantom is 1540 m/s. The model attenuation coefficients in the sample and reference phantom are 0.559 dB/cm-MHz and 0.573 dB/cm-MHz respectively (horizontal line).
Similar trends in the results from the 1580m/s sample phantom are observed in Fig. 9.2 for the different Cases. Notice in this example, the large bias in results at the 2cm transmit focal depth are in the opposite direction as that for the 1500m/s case due to the opposite sound speed difference between the sample and reference. The significant improvements observed for Case IV again are observed.

![Graphs showing attenuation coefficients vs. frequency for different cases.](image)

**Figure 9.2.** Slopes of attenuation coefficient vs. frequency over the ROI with a 2cm transmit focal distance, for all four experimental cases (Cases I, II, III, IV) shown on each graph. Subplot (a) is from simulated data while subplot (b) shows results from experiments. The sound speed in the sample is 1580m/s and that in the reference phantom is 1540m/s. The model attenuation coefficients in the sample and reference phantom are 0.591dB/cm-MHz and 0.573dB/cm-MHz respectively (horizontal line).

Absolute percent errors for the different data acquisition and analysis cases summarized in Table 9.2 are presented in Fig. 9.3 for the 1500m/s phantom and in Fig. 9.4 for the 1580m/s phantom. In each figure, the top row of plots presents results from simulations while the bottom row shows experimental results. Each sub plot includes five curves to display results for each of the five different transmit focus locations.
As can be seen in all Case I results from simulations (upper rows in Figs. 9.3 and 9.4), a significant bias in the estimated attenuation results occurs near the transmit focus. The bias is larger at deeper transmit focus settings, except for the 7cm focus setting. Experimental data from the two sample phantoms are presented in the lower rows in Figs. 9.3 and 9.4. The general trend in the experimental data follows that seen with simulations, where the bias is the greatest near the transmit focal depth and it is reduced by applying the corrections outlined in Table 9.2. In both results from simulation and experiment, Case IV, in which the sound speed used in the beam former and the sound speed assumed in the depth calibration matched the sound speed of the sample, exhibits the smallest fluctuation over the ROI for both the experimental and simulation results at any focal depth setting. The experimental results exhibited less variation among the four Cases than the simulation results, possibly because of the use of multiple independent frames for computing the attenuation.
Figure 9.3. Absolute percent error of slopes of attenuation coefficient vs. frequency from Cases I, II, III, and IV (from left to right), derived from simulation (top row) and experimental (bottom row) data, where $c_{sam} = 1500$m/s and $c_{ref} = 1540$m/s: Case I, where no corrections are applied, i.e. $c_{bf} = 1540$m/s for both sample and reference and $z_{sam} \neq z_{ref}$; Case II, where $c_{bf} = 1540$m/s for both sample and reference but $z_{sam} = z_{ref}$; Case III, where $c_{bf}$ matches each of $c_{sam}$ and $c_{ref}$ but no depth correction is applied, $z_{sam} \neq z_{ref}$; Case IV, where $c_{bf}$ matches each of $c_{sam}$ and $c_{ref}$ AND sound speed corrections are used to match distances, $z_{sam} = z_{ref}$. The transmit focus settings were 2cm, 3cm, 4cm, 5cm, and 7cm. The model attenuation coefficients in the sample and reference phantom are 0.559dB/cm-MHz and 0.573dB/cm-MHz, respectively.

Figure 9.4. Absolute percent error of slopes of attenuation coefficient vs. frequency from Cases I, II, III, and IV (from left to right) derived from simulation (top row) and experimental (bottom row) data, where $c_{sam} = 1580$m/s and $c_{ref} = 1540$m/s: the Case conditions are outlined the figure 3 caption. The transmit focus settings were 2cm, 3cm, 4cm, 5cm, and 7cm. The model attenuation coefficients in the sample and reference phantom are 0.591dB/cm-MHz and 0.573dB/cm-MHz, respectively.

The attenuation coefficient was generally underestimated for the 1500m/s phantom and overestimated for the 1580m/s phantom when no corrections were applied. The mean error, obtained by averaging over depth and considering all transmit focus locations, was -4.3% for the
1500m/s phantom and 5.0% for the 1580m/s phantom. These were computed from the simulated data.

Interestingly, no significant difference among the four acquisition and analysis cases was observed in the results obtained using the 7cm transmit focus location. Evidently, when using a transmit focal zone where the focal depth is significantly greater than the transducer aperture and its location is beyond the ROI, the errors caused by mismatched sound speeds in the reference and sample are smaller than for the shallow transmit focus conditions. Focusing effects over the ROI are much more gradual for the 7cm depth than for the other transmit focal depths, minimizing the bias errors.

9.4 Discussion

The RPM has been shown to provide accurate results for attenuation and backscatter coefficients estimated using clinical ultrasound equipment when the speed of sound in the reference closely matches that of the sample. The focus of this paper was on the accuracy of the method when the sound speed in the reference media used to account for system dependencies on the data differs from the sound speed in the sample.

Three observations are noted. First, for either a sample having a sound speed of 1500m/s or 1580m/s, where the reference phantom’s sound speed is 1540m/s, a bias existed in the attenuation estimates, particularly near the transmit focus location. Secondly, this bias near the transmit focus was larger (the maximum error was higher) at deeper focus settings. Finally, the bias near the transmit focus location has different trends for the 1500m/s sample results
compared to those for the 1580m/s sample; i.e., the depth dependent oscillations in attenuation estimations are in opposite directions for the two cases.

Possible explanation of these observations is the difference in spatial power distribution between the sample and reference caused by a small difference in the location of the focus accompanying the difference in speeds of sound in the sample and reference media. To visualize these power distribution differences, another set of simulations was done. Most conditions were the same as those applied in simulations described above, with the sample having either a 1500m/s or a 1580m/s sound speed, the reference phantom having a sound speed of 1540m/s, and the linear array dimensions matching those of the transducer used in the experiment. However, now the sample and reference media had identical attenuation properties, 0.6dB/cm-MHz.

Power spectra were calculated from the sample and reference echo data applying both Cases I and IV as described in Table 9.2. Then the log of the ratio of the power from the sample to that from the reference was obtained by integrating echo signal power spectra over the 4-8MHz frequency range. These power ratios were computed over the whole ROI and displayed as images. Results are shown in Fig. 9.5 for Case I (left column) and Case IV (right column) and are presented for transmit focus locations of 2cm, 4cm, and 7cm.

Comparing the left column (Case I) with the right column (Case IV), since the sample and reference have the same attenuation and backscatter coefficients for this simulation, the expected log ratio is 0dB throughout the image. The log ratio in Case IV exhibited a consistent pattern throughout the depth range, closer to 0dB than that in Case I. Figures 9.5(a), and 9.5(c)
depict a clear bias near the transmit focus location, resulting in a banding of the imaged sample-to-reference phantom power spectra ratios. The banding is more prominent in Fig. 9.5(c), where the transmit focal depth is deeper, than in Fig. 9.5(a). The banding disappears for simulated data acquired when the speed of sound assumed in the beam former closely matches that in the reference or sample media and actual sound speeds in the sample and reference are used to assure that power spectra ratios are from precisely the same depth, as done for Case IV.

The banding near the transmit focus location is caused by the slight mismatch of the locations of the focal peak in the signals from the sample and those from the reference media. The actual focal depth in the 1500m/s phantom is slightly deeper than that in the reference medium whose speed of sound is 1540m/s and slightly shallower in the 1580m/s phantom.\(^{18}\) Beyond the focus, the energy in the beam spreads gradually, further weakening the received signal. The weakening process occurs more rapidly with depth when the focal depth is closer to the transducer, as in the 1580m/s sample, than when it is deeper (1500m/s sample). This is consistent with the observation that the average attenuation coefficients were under estimated by 4.3% for the 1500m/s sample but over estimated by 5.0% for the 1580m/s sample. This also explains why the bias trends near the transmit focus location in the 1500m/s phantom and 1580m/s phantom are in opposite directions.

The effects of a mismatch in the sound speed in the sample and reference media is not necessarily peculiar to the RPM, but likely occurs for any attenuation estimation method where power spectra ratios of sample to reference are employed to eliminate system dependent factors.
Thus, methods where system calibrations are done using planar reflectors in water, for example, should be evaluated in a similar fashion.
Figure 9.5. Images from simulations depicting ratios of integrated echo signal power spectra from a sample to that from corresponding locations in a reference phantom. The sample and reference phantom have identical attenuation and backscatter coefficients, but $c_{\text{sam}} = 1500\text{m/s}$ and $c_{\text{ref}} = 1540\text{m/s}$. The ratio values are expressed in dB. (a) Case I with transmit focus at 2cm (b) Case IV with transmit focus at 2cm (c) Case I with transmit focus at 4cm (d) Case IV with transmit focus at 4cm (e) Case I with transmit focus at 7cm (f) Case IV with transmit focus at 7cm.

When estimating attenuation coefficients in tissues, in most cases the sound speed in the sample will not be known exactly. Some ultrasound imaging instruments vary the beamformer sound speed depending on the tissue scanned, and use of such a feature may enable better estimates of parameters determined using a reference phantom. Another possibility is to use instruments that provide sound speed optimization routines, either through automated methods or by allowing the operator the choice of “dialing in” the most appropriate beamformer sound speed, when doing attenuation estimations such as these. Future studies will investigate the ability of these algorithms to supply accurate values for correcting the RPM following our Case IV approach.

Compared to examples shown in Figs. 9.5(a), 9.5(c) and 9.5(e), horizontal banding is minimized in Fig. 9.5(e) where the transmit focus is at 7cm. This is consistent with results in
Figs. 9.3 and 9.4, where errors caused by different sound speed values in the sample and reference appear to be lowest when the transmit focal zone is beyond the ROI for which attenuation coefficients are determined. With the transmit focus well beyond the ROI, evidently focusing differences in the sample and reference are not as significant. Alternatively, applying more weakly focused transmissions might also minimize the focal zone bias errors. These conditions will be explored more thoroughly in future reports.

In Figs. 9.3 and 9.4, the experimental results exhibited higher percent errors than simulation results for Case IV. One possible cause is the existence of electronic system noise in the RF data from the experiment. The simulated RF data did not include random noise which could have been present in the experimental data. Another possible cause for higher (apparent) errors in attenuation estimates from backscattered echo data is the linear dependence on frequency assumed from the narrowband substitution method. In the case of simulations, attenuation with perfect linear frequency dependence was applied. Finally elevational focusing in the clinical imaging system could have played a role in addition to electronic focusing in the image plane. Since this elevational focusing was done mechanically, the diffraction difference in the sample and reference caused by this focusing and sound speed mismatch is not accounted for in Case IV. Elevational focusing was not used in the simulations.

## 9.5 Conclusion

Differences between the speed of sound in a sample and that assumed in the beamformer as well as between the sound speed of a sample and that of reference medium cause biases in RPM attenuation measurements. With array systems, the bias is greatest near the transmit focus.
location. Biases are reduced or eliminated by matching the sound speed assumed in the beamformer to that of the medium and taking care to match power spectra in the sample and reference from precisely the same depth. If the sound speed of the sample is unknown, setting the transmit focus location further from the sample minimizes biases in attenuation estimates.

9.6 References


Chapter 10:
Future Work

In this chapter, future directions are suggested in five areas: attenuation estimations, backscatter coefficient (BSC) estimations, effective scatterer diameter (ESD) estimations, the impact of a sound speed mismatch between the tissue and the reference phantom, and the use of QUS for differentiation of breast masses. The proposed topics to investigate in each area are suggested separately below.

Attenuation estimation

The current limitations in estimating the attenuation of in vivo breast masses are the size and the heterogeneity of the region of interest (ROI). The reference phantom method\(^1\) (RPM, see Section 2.1.1) has produced accurate attenuation estimates with small variance from tissue-mimicking phantoms. Such results may have been possible because in the case of phantoms sample data can be obtained from a large, homogeneous ROI. Moreover, several independent frames of RF echo data usually can be obtained from a phantom.

To improve the precision of attenuation estimates in breast masses, angular compounding can be considered. The work presented in this dissertation used radiofrequency (RF) echo data acquired from a \(0^\circ\) angle, where a region is interrogated only once for each acquisition. Compounding the data processed from RF signals acquired from other angles can be utilized in the future.
Deformation compounding\(^2\) is another approach to obtaining multiple decorrelated observations of the echo signal power spectrum from small regions of interest. The approach combines the technology of elasticity imaging (tracking motion of a small ROI following deformation) with standard techniques for spectral estimation. Deformations, as small as ones producing only a 2\% strain, create uncorrelated power spectral estimates for averaging. Thus, compounding the data processed from RF signals acquired from small deformations can also be utilized in the future.

The heterogeneity of a breast mass can create two difficulties. The first is in finding a homogeneous region to apply the RPM, and the other is in representing an attenuation value for a specific mass. If the homogeneous region within the breast mass is not large enough to properly evaluate the change of the power spectrum ratio with depth, other attenuation estimation methods, such as the narrowband video signal analysis method\(^3\) (which uses the time-domain signal) can be useful. Another option is using a different window in applying the RPM. Currently, our lab is investigating the relationship between window size, bias, and the variance of the power spectral density (PSD) function with several windowing functions.\(^4\) According to Rosado-Mendez’ preliminary analysis, a modern spectral analysis method incorporating a multi-taper function gives lower variance PSD estimates with the same window size than does the Hann window function. Another approach would be to investigate frequency analysis methods other than the short-time Fourier transform to estimate the power spectrum to determine which method gives a more accurate power spectrum estimate with a small segment of RF data. Examples include the discrete/continuous wavelet transform.
Backscatter estimation

The accuracy of the BSC estimated by the reference phantom method (see Section 2.3) depends on the accuracy of the power spectrum and of the compensation for attenuation over the path between the transducer and the ROI. Regarding the power spectrum estimation, the approaches suggested above for improving attenuation estimations can be considered here as well.

In Chapter 8, to account for the attenuation up to the ROI when analyzing in vivo data, a Least Squares Method (LSM, see Chapter 7) was used. The LSM was verified with phantom studies, where results were compared with results from the reference phantom method and with known properties of the materials. However, the LSM has not been compared to other attenuation estimation methods for in vivo breast data. Recently Bigelow et al.\(^5\) developed a method for total attenuation estimation. Thus a comparison of effective attenuation estimates done using the LSM and the method developed by Bigelow et al.\(^5\) would be valuable. Furthermore, the accuracy of the LSM should be evaluated by measuring attenuation and backscatter coefficients within masses contained in challenging anthropomorphic breast phantoms, starting with ACR breast phantoms developed by Madsen.\(^6\) These phantoms incorporate undulating layers of tissue-mimicking fat to nonfat, which distort ultrasound beams in a fashion analogous to human breast tissue.

The LSM models the effective attenuation as a linear function of frequency. However, it is plausible for inhomogeneous layers to have an attenuation coefficient that exhibits non-linear frequency dependence. Thus for the LSM application, using a small segment of frequency range
within the usable bandwidth of the transducer may be preferred. This approach may also be helpful to improve the accuracy of the simultaneous BSC estimation using the LSM, since the BSC is modeled as following a simple power law function.

*Effective scatterer diameter estimation*

The estimated ESDs for breast masses in Chapter 8 were within a range of 40-70μm. This may have been due to the limited frequency range available with the current clinical transducers. In a study to evaluate ESD differences between fibroadenomas and carcinomas in an animal model, the ESD from tumors ranged from 0-160μm. Furthermore, Insana et al. suggested that ka (where k is the wave number and a is the scatterer radius) should be less than 1.2 for reliable ESD estimations using the Gaussian model. Thus for the future, a broader bandwidth will be required to search for the ESD over a broader size range and to investigate the ESD as a differential biomarker.

Any increase in the data bandwidth is dependent on the imaging system’s capabilities. However, the current frequency range applied for ESD estimations of human breast masses is limited because we chose the frequency range resulting in the largest ROI from four data sets (as described in Section 8.2.2), and the data collected with low (7MHz) and high (15MHz) center frequencies were combined. If we utilize only the data acquired with the high center frequency, which usually gives a broader bandwidth, the overlapped frequency range can be increased with a trade-off of the size of the ROI.

The ESD estimates can also be improved by increasing the number of independent scans of sample and reference data to generate the BSC. Thus, compounding the data (from different
angles or after deformations) can be considered as well as increasing the number of scans of the reference phantom.

*Sound speed mismatch*

Results in Chapter 9 show that biases occur when measuring the attenuation coefficient of a sample that has a speed of sound 3% lower, or 3% higher than that of the reference phantom when the reference speed of sound is 1540 m/s. Although only sound speed mismatch effects on attenuation estimations are presented in Chapter 9, backscatter coefficient vs. frequency and ESD estimates would be affected as well since these are also determined from the power spectra ratio as mentioned in Section 9.4.

In Chapter 9, locating the transmit focus distal to the ROI was suggested for cases where the speed of sound of the sample is unknown. However, the ideal case would be when we can estimate the sample’s sound speed and make appropriate adjustments to the speed of sound assumed in the system beamformer. While we cannot adjust the sound speed setting for the beamformer for each part of the medium, knowing the sound speed in the medium would improve the accuracy of the power spectrum ratio by assuring the power spectrum of the sample and reference are from the same depth and setting the time delay in the beamformer to be the approximate medium sound speed. Though the results are not presented in this dissertation, a preliminary experiment was done for the sound speed estimation using simulation data. When the assumed sound speed in the beamformer matches that of the sample, the integrated power over the available bandwidth was higher than that from the mismatched sound speed cases. If the sound speed in the beamformer can change within the range of speeds, which can be predicted
with some previous knowledge of the sample, the sound speed of the medium might be estimated by comparing the magnitude of integrated power from each case.

**Differentiation of breast masses**

In Chapter 8, the combination for the averaged backscatter coefficient (ABSC) and attenuation coefficient showed the potential to differentiate fibroadenomas from carcinomas. In the future, not only these parameters but other features used in breast mass assessments with ultrasound, such as the mass boundary, shape, and the ratio of boundary size in B-mode to that in elastography,\(^\text{10}\) can be included.

10.1 References


