CHAPTER 1
INTRODUCTION TO THE *IN VIVO* ESTIMATION PROBLEM

Over the past several decades there has been an explosion of new medical imaging modalities. Also, established technologies, such as X-ray, have opened up new imaging methods such as CT scans that allow for even greater diagnostic potential. Due to the number of different imaging techniques, an imaging system may not remain competitive in the clinical environment if it only provides the clinician with a qualitative image showing the placement of the patient's tissue. Structure and/or function of the tissue in question must also be obtained to enhance the detection and diagnosis of medical problems. In medical ultrasound, obtaining this type of information is both directly and indirectly related to the estimate of the *in vivo* power spectrum on a patient specific basis.

1.1 Motivation: The Need to Know the *In Vivo* Power Spectrum

In the past, medical ultrasound has distinguished itself in functional imaging by providing real-time images of tissue motion. Furthermore, Doppler ultrasound allows measurements and images to be made of blood flow, allowing the clinician to diagnose many different disease states [*Routh*, 1996]. Also, the impact and use of Doppler ultrasound and related techniques will only increase as microbubble contrast agents are introduced into the blood stream to assess perfusion conditions in the brain, tumors, and other organs [*Wilkening et al.*, 1999; *Wilkening et al.*, 2000; *Simpson et al.*, 2001].

Although the benefits provided by Doppler ultrasound and related techniques are significant, the increased exposure levels required introduce the potential for damaging bioeffects [*Barnett*, 2001]. Of particular importance is the heating near the developing cranial bone of the fetus because heating of the developing brain tissue could potentially result in long-term neurological disorders. The heating is difficult to predict due to the nonlinear propagation

of the ultrasound in the embryonic fluid [*Bacon and Carstensen*, 1990] as well as the changing absorption characteristics of the developing fetal skull [*Barnett*, 2001]. In the past, these heating concerns have been addressed by requiring that the output levels be kept much less than that anticipated to produce biologically significant temperature increases. However, allowing greater output power levels would improve the diagnostic capability of the ultrasound system. As a result, the FDA (Food and Drug Administration, Center for Devices and Radiological Health) now allows the developing fetus to be exposed to nearly 8 times the traditional dose, provided that the equipment provides a real-time output display of the potential risk [*Barnett*, 2001]. Unfortunately, the accuracy of the current estimates of temperature rise have been shown to be poor [*Barnett*, 2001; *Horder et al.*, 1998, *Wojcik et al.*, 1999] due to uncertainties in the total frequency-dependent attenuation along the propagation path (i.e., *in vivo* power spectrum) and absorption coefficient. The absorption coefficient measures the rate at which energy is absorbed by the medium as the wave propagates and is often assumed to be the same as the attenuation coefficient for most tissues [*NCRP*, 1992]. The attenuation coefficient measures the rate at which energy is lost from the wave (i.e., from both scattering and absorption) as the wave propagates. Hence, knowing the *in vivo* power spectrum on a patient specific basis would improve our estimates of temperature rise.

As well as using ultrasound to image function, many investigators have also attempted to quantify the structure of the tissue from the ultrasound images. Quantifying the tissue microstructure to aid in tumor diagnosis is of particular interest. *Lizzi et al.* [1983; 1997a] pioneered some of this work by comparing the backscattered spectrum from ocular masses to a reference spectrum in order to assess disease states. The tissue was then characterized by fitting a line to the calibrated power spectrum, relative to the reference spectrum, and determining the spectral slope (dB/MHz), the spectral intercept (dB, extrapolation to 0 MHz), and the midband fit (dB, value of fit at center frequency) [*Lizzi et al.*, 1997a]. Lizzi was successful due to the negligible frequency-dependent attenuation along the propagation path leading to the ocular mass. Hence, the changes in the calibrated backscattered spectrum were due entirely to the microstructure of the ocular masses and were not influenced by the intervening tissue. Before the scattering properties of embedded tumors can be estimated, the total frequency-dependent attenuation along the propagation path (i.e., *in vivo* power spectrum) must be known on a patient-specific basis [*Lizzi et al.*, 1983].

While quantifying the size and acoustic concentration of scatterers within tissue has historically been a popular method to quantify tissue structure, other methods such as elastography, sonoelasticity, and acoustic radiation force impulse imaging (ARFI) are being developed. In general, these methods involve applying a force to a region of tissue and then using ultrasound to measure the resulting displacement. If the magnitude of the force is known, the mechanical properties such as the Young's modulus of the tissue can be measured. Of particular interest is ARFI which involves using one acoustic signal to provide the force using radiation force, and a second acoustic signal to measure the displacement [*Nightingale et al.*, 2000]. Assuming that the forcing field is a plane wave, the resulting radiation force would be given by

$$F_R = \frac{2\alpha_{loc} I}{c}, \tag{1.1}$$

where I is the temporal-average intensity, α_{loc} is the local absorption coefficient of the medium, and c is the speed of sound in the medium [*Nightingale et al.*, 2000]. Hence, in order for the magnitude of the applied force to be known and the stiffness of the tissue quantified, both the intensity (i.e., *in vivo* power spectrum after attenuation along propagation path) and the local absorption must be estimated. Also, because the force in ARFI is applied using an acoustical signal, there is a greater potential for temperature related bioeffects [*Nightingale et al.*, 2000], so ARFI could also benefit from accurate real-time *in vivo* temperature rise monitoring.

Clearly, many different aspects of medical ultrasound would benefit from accurate estimates of the *in vivo* power spectrum. Hence, this investigation attempted to improve the reliability and accuracy in making estimates of the power spectrum by estimating the attenuation along the propagation path using algorithms that could be later implemented on a patient specific basis.

1.2 Background: Previous Approaches

Due to the significance of estimating the power spectrum *in vivo* for many different aspects of medical ultrasound, a wide variety of approaches have been used by previous investigators. A description of the previous approaches along with a discussion of the shortcomings of each approach is provided below.

1.2.1 Neglect patient variation

The most common approach in the past, especially with regard to estimating temperature rise, is to assume that the attenuation with distance along the propagation path and the local absorption at the location of interest are exactly the same for every patient that will ever be imaged. This is the basis for the traditional Thermal Indices (TI's), used to predict ultrasound-induced heating, and the Mechanical Index (MI), used to estimate the potential for nonthermal bioeffects [*Abbott*, 1999; *AIUM/NEMA*, 1998]. The indicators are found by measuring the output of the ultrasound source in a water bath and then derating the measured values by 0.3 dB/cm/MHz to predict the *in vivo* power spectrum [*Abbott*, 1999]. The local absorption coefficient is also assigned a value depending on whether or not bone is in the region of interest [*Abbott*, 1999]. As a related issue, the current TI's only predict the steady-state temperature increase while neglecting the exposure time required to reach this increase. Hence, others have proposed that the exposure time also be included when predicting the resulting temperature rise for safety considerations [*Lubbers et al.*, 2003; *Nightingale et al.*, 2000]. Although most common when predicting temperature increases, the neglecting of patient variability has also been used in studies involving the characterization of tissue microstructure. *Oelze and O'Brien* [2002b] assumed that the rat tissues always had an attenuation coefficient of 0.9 dB/cm/MHz when forming their microstructure images of rat tumors.

The obvious problem with this approach is that the attenuation and absorption coefficients between patients and between different locations in the same patient are not constant. As an example, consider a study of 24 patients with nonviable, first trimester pregnancies as reported by the *AIUM* [1993]. In the study, the measured attenuation coefficient for the abdominal wall varied from 0.39 ± 0.25 dB/cm/MHz for patients with a full bladder to 0.57 ± 0.37 dB/cm/MHz for patients with an empty bladder. Hence, the potential exists for patient variability as high as 0.8 dB/cm/MHz depending on the state of the patients' bladder. In another study that measured the ultrasound signals *in vivo*, the total attenuation along the propagation path from the abdominal wall through the vagina was measured 90 different times using 57 different subjects with empty bladders and 161 different times using 64 subjects with full bladders [*Siddiqi et al.*, 1999]. In this study, the total attenuation coefficient varied from 0.8 ± 0.4 dB/cm/MHz for the empty bladder to 0.6 ± 0.3 dB/cm/MHz for the full bladder.

As well as the gross differences in attenuation along the propagation path that can occur, there are also differences in the attenuation within the same tissue type between patients as is evident in the results reported by *Goss et al.* [1980]. In two different studies reported by Goss, the attenuation coefficient for human liver (typical of soft tissue) was reported at 0.7 ± 0.2 dB/cm/MHz and 1.32 ± 0.3 dB/cm/MHz. Hence, the attenuation coefficient in liver can vary by more than 1.1 dB/cm/MHz. Likewise, in a study done by *Wear* [2001a], the slope of the attenuation coefficient versus frequency of 16 human calcaneus bone samples was measured at 12.86 ± 4.79 dB/cm/MHz, further emphasizing the variability in attenuation coefficient in the same tissue type.

1.2.2 Total attenuation from the spatial decrease in backscattered intensity

Another method for determining the total attenuation along the propagation path in the past, hence the *in vivo* power spectrum, involved compensating for the spatial decrease in backscattered intensity by varying the assumed attenuation until the noise-to-signal ratio of the echo envelope peaks from the source to the depth of interest was minimized [*He and Greenleaf*, 1986]. The noise in this case was the standard deviation of the echo envelope peaks and the signal was the mean value of the echo envelope peaks. In this way, a single attenuation coefficient was determined for all the tissue along the propagation path. Obviously, the best estimates would be obtained if the tissue were homogeneous. Heterogeneities in the tissue would yield errors in the attenuation estimate. *He and Greenleaf* [1986] also mentioned that their theory would break down in the presence of specular reflections arising from vessel walls. Hence, it is unlikely that their technique would work robustly in a clinical setting.

1.2.3 Total attenuation by ray method

Another method for estimating the total attenuation along the propagation path and the resulting *in vivo* power spectrum involved making estimates of the local attenuation throughout the tissue region for every tissue type. Then, rays could be traced back from the region of interest to the source. The total attenuation was then found by summing up the local attenuations along each ray path [*Lizzi et al.*, 1992; *Sidney*, 1997]. This algorithm suffers from two potential pitfalls. First, it is difficult to determine the local attenuation near the surface of the ultrasound source. Second, errors in estimating the local attenuation would be compounded as the rays

moved deeper into the tissue. *Sidney* [1997] was able to achieve good performance using this approach in simulations, but he assumed that the local attenuation was known exactly when, in a clinical setting, it would also need to be estimated.

1.3 Approach and Summary of Results

Clearly, the problem of determining the *in vivo* power spectrum has not been solved. In fact, it could be argued that the problem has been largely ignored. During the course of this investigation, an entirely new approach to estimate the *in vivo* power spectrum was implemented by considering the physics of the backscattered waves while assuming a model for the intended targets. Because the model for the targets is strongly dependent on the intended application for the ultrasound, the work focused on the spectral estimates as they apply to quantifying the size of the scattering microstructure (i.e., scatterer) for the purpose of tissue diagnosis. However, some of the background work for predicting the temperature increase at the bone/brain boundary when exposed to focused ultrasound is addressed in Appendices A, B, C, and G.

Before the estimation approach related to quantifying the tissue microstructure can be discussed, the assumptions involving the backscatter need to be understood. The research did not intend to validate any of the traditional assumptions, but rather improvements in tissue characterization were made within the existing framework. However, the developed algorithms still retained enough flexibility to be adapted if new discoveries require the modification of these assumptions. The fundamental assumption when characterizing the backscatter from biological tissues is that the scattering sites are randomly positioned throughout the tissue region of interest without any multiple or coherent scattering, and the region of interest is within the focal region for the ultrasound source [*Insana et al.*, 1990]. Furthermore, it is assumed that the form of the acoustical impedance, or form factor $F_\gamma\left(\omega, a_{eff}\right)$ for the scatterer, is known (i.e., model for the intended targets) and that only one type of scatterer exists in the tissue region [*Insana et al.*, 1990]. One common form factor assumed for tissue is the Gaussian form factor where the acoustical impedance of the scatterer falls off according to a Gaussian distribution [*Oelze and O'Brien*, 2002a; *Insana et al.*, 1990]. The Gaussian form factor could also be used to model tissue containing a distribution of scatterer sizes about a common mean. Due to its past popularity, the Gaussian form factor was used in all of our computer simulations modeling tissue. In addition to these assumptions, the developed algorithms for estimating scatterer size

neglected the effects of focusing along the beam axis. Hence, before developing the algorithms for estimating the scatterer size and attenuation along the propagation path, the equations were rederived to allow for the focused sources used in modern clinical ultrasound.

Based on these assumptions and the associated physics of the backscattered signals, two algorithms were proposed and evaluated regarding their ability to estimate the total attenuation along the propagation path (i.e., *in vivo* power spectrum) and scatterer size simultaneously. The first algorithm investigated assumed that the backscattered spectrum could be accurately modeled as a Gaussian distribution, the total attenuation had a linear frequency dependence, and the form factor for the scatterer had the form e^{-Af^n} where A is some known constant times the scatterer size and $n \geq 2$. With these assumptions, the Gaussian bandwidth of the backscattered power spectrum is only affected by the scatterer size, and, after correction for the scatterer size, the center frequency is only affected by the total attenuation. The algorithm yielded acceptable results for attenuations less than 0.25 dB/MHz (i.e., 0.05 dB/cm/MHz), but higher values of attenuation had very poor performance. The degradation in performance resulted from the spectra not being a perfect Gaussian. As the attenuation was increased the Gaussian bandwidth of the backscattered power spectrum was reduced by the attenuation. Hence, the scatterer size estimates were corrupted at the higher values of attenuation.

From the first algorithm, it was evident that the total attenuation and scatterer size needed to be considered simultaneously. Hence, in the second algorithm, the total attenuation and scatterer size were found using a two-parameter minimization routine over the entire spectrum similar to the traditional algorithm used previously to find just the scatterer size [*Insana et al.*, 1990]. Furthermore, the algorithm made no assumptions about the backscattered spectra or the frequency dependence of the attenuation. It only assumed that the frequency dependence and form factor were known. The algorithm gave good accuracy and precision for the attenuation estimate provided that a large enough frequency range (largest frequency minus smallest frequency) was used in the minimization. Likewise, the algorithm gave good accuracy and precision for the scatterer size estimate when the frequency range multiplied by the scatterer size was sufficiently large.