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● *Original Contribution*

SCATTERER NUMBER DENSITY CONSIDERATIONS IN REFERENCE PHANTOM-BASED ATTENUATION ESTIMATION

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Abstract—Attenuation estimation and imaging have the potential to be a valuable tool for tissue characterization, particularly for indicating the extent of thermal ablation therapy in the liver. Often the performance of attenuation estimation algorithms is characterized with numerical simulations or tissue-mimicking phantoms containing a high scatterer number density (SND). This ensures an ultrasound signal with a Rayleigh distributed envelope and a signal-to-noise ratio (SNR) approaching 1.91. However, biological tissue often fails to exhibit Rayleigh scattering statistics. For example, across 1647 regions of interest in five *ex vivo* bovine livers, we obtained an envelope SNR of 1.10 ± 0.12 when the tissue was imaged with the VFX 9L4 linear array transducer at a center frequency of 6.0 MHz on a Siemens S2000 scanner. In this article, we examine attenuation estimation in numerical phantoms, tissue-mimicking phantoms with variable SNDs and *ex vivo* bovine liver before and after thermal coagulation. We find that reference phantom-based attenuation estimation is robust to small deviations from Rayleigh statistics. However, in tissue with low SNDs, large deviations in envelope SNR from 1.91 lead to subsequently large increases in attenuation estimation variance. At the same time, low SND is not found to be a significant source of bias in the attenuation estimate. For example, we find that the standard deviation of attenuation slope estimates increases from 0.07 to 0.25 dB/cm-MHz as the envelope SNR decreases from 1.78 to 1.01 when estimating attenuation slope in tissue-mimicking phantoms with a large estimation kernel size (16 mm axially × 15 mm laterally). Meanwhile, the bias in the attenuation slope estimates is found to be negligible (<0.01 dB/cm-MHz). We also compare results obtained with reference phantom-based attenuation estimates in *ex vivo* bovine liver and thermally coagulated bovine liver. (E-mail: Rubert@wisc.edu)

Key Words: **Attenuation, Envelope signal-to-noise ratio, Scatterer number density, Reference phantom, Thermal ablation, Liver, Multi-taper.**

INTRODUCTION

Ultrasound imaging is a low-cost, portable imaging modality, and attenuation coefficient estimation and subsequent imaging have the potential to be a valuable tool for several clinical applications, including distinguishing between different types of breast masses (Nam et al. 2013), characterizing bone density to assess the risk of osteoporosis and bone fracture (Sasso et al. 2008; Wear 2003), diagnosing fatty infiltration in the liver (Narayana and Ophir 1983) and indicating the extent of thermal ablation therapy in the liver and other abdominal organs (Bush et al. 1993; Gertner et al. 1997; Kemmerer and Oelze 2012; Parmar and Kolios 2006; Techavipoo et al. 2004). In this article we focus on attenuation estimation in the liver and its application to assessment of the extent of thermal coagulation after thermal ablation therapy. Attenuation in thermally coagulated regions has often been found to approximately double relative to that in untreated normal liver tissue (Bush et al. 1993; Gertner et al. 1997; Kemmerer and Oelze 2012; Parmar and Kolios 2006; Techavipoo et al. 2004).

In particular, Parmar and Kolios (2006) found a relative increase in attenuation by a factor of 2.29 at a transmit center frequency of 5 MHz in *ex vivo* porcine liver after it was heated to 75°C for 60 min. Bush et al. (1993) estimated increases in attenuation coefficient in the frequency range 3.0 to 8.5 MHz from 32% to 192% in high-intensity focused ultrasound (HIFU) lesions approximately 10 × 30 mm in cross section in *ex vivo* pig livers. Gertner et al. (1997) found that the attenuation coefficient estimated at 3.5 MHz increased by a factor >1.8 in eight store-bought bovine liver samples after 30 min of heating at 70°C in a saline bath. Techavipoo

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et al. (2004) examined the temperature dependence of sound speed and attenuation in canine liver tissue and found that the attenuation coefficient decreased slightly as tissue was heated up to 50°C and then increased as tissue was heated from 50°C to 100°C. The relationship between temperature and attenuation was hypothesized to be due to tissue coagulation increasing tissue attenuation and temperature elevation decreasing tissue attenuation (Techavipoo et al. 2004). Kemmerer and Oelze (2012) found that the attenuation slope doubled from 0.2 to 0.4 dB/cm-MHz over the frequency range 9–25 MHz when rat liver tissue was exposed to a 70°C saline bath. In these experiments, gas bubbles produced by heating were addressed very differently. In the saline bath experiments of Gertner et al. (1997), the authors stated that the tissue was degassed only before heating, whereas in the other saline bath heating experiments, tissue degassing was not explicitly mentioned (Kemmerer and Oelze 2012; Parmar and Kolios 2006; Techavipoo et al. 2004). In the HIFU experiment described in Bush et al. (1993), tissue was degassed under vacuum both before and after HIFU exposure.

A variety of techniques have been applied to estimate attenuation within tissue. Several authors have proposed time-domain algorithms (Ghoshal and Oelze 2012; He and Greenleaf 1986; Jang et al. 1988; Knipp et al. 1997). He and Greenleaf (1986) proposed the envelope peak method, where the ratio of the mean envelope peak to standard deviation of envelope peaks over depth was minimized by adjusting an attenuation-dependent gain function. Jang et al. (1988) also proposed applying an attenuation- and depth-dependent gain to the signal envelope to determine attenuation. In their method, the entropy difference between adjacent signal segments was minimized by adjusting the attenuation estimate and an associated depth-dependent gain function. Knipp et al. (1997) proposed a method for estimating attenuation and backscatter in an unknown sample by comparing B-mode image values with values in a look-up table developed for individual transducers from phantoms with known attenuation and backscatter coefficients. This method had the disadvantage of requiring determination of an effective frequency to assign to the recorded B-mode image to account for frequency dependence of beamforming, backscatter and attenuation. Ghoshal and Oelze (2012) recently proposed a time-domain algorithm where they explicitly modeled the diffraction pattern for a single-element circular transducer and iteratively solved for the attenuation coefficient in an unknown sample.

Frequency-domain techniques are currently the more popular method for determining the attenuation coefficient in tissue. Frequency-domain techniques are frequently described in analogy to two techniques explored by Kuc (1984): the spectral shift method and the spectral difference method. In Kuc's (1984) approach, the ultrasound signal before propagating through tissue is modeled by a pulse power spectrum, $P_i(f)$. The effect of traveling through a thickness of tissue, D, is to multiply the pulse power spectrum by an attenuation transfer function, $|H(f)|^2 = \exp(-4\pi\beta fD)$, where the attenuation coefficient is assumed to have a linear frequency dependence. After making a round trip through tissue, the pulse power spectrum is then given by $P_f(f) = P_i(f)\exp(-4\pi\beta fD)$.

In the spectral shift method, $P_i(f)$ is modeled by a Gaussian function, and the effect of attenuation is to shift the center frequency of the Gaussian spectrum by an amount proportional to β. The attenuation coefficient can then be obtained by tracking the center frequency of the ultrasound pulse with depth. In the spectral difference method, the logarithm of the ratio of the power spectral magnitude is examined. To estimate β, log spectral ratios are directly computed and no parametric model for the pulse spectrum is necessary. The spectral shift and spectral difference techniques as described by Kuc (1984) failed to account for the effect of transducer beam diffraction and focusing effects. Insana et al. (1983) developed correction factors to the spectral difference method to account for beam diffraction when making attenuation measurements in tissue-mimicking (TM) phantoms with known attenuation coefficients. Madsen et al. (1984) derived a frequency-domain model for the echo signal voltage for measurements of backscatter coefficients. This model was applied to estimation of backscatter using single-element transducers, where beam diffraction was accounted for using the signal spectrum from reflections off a reference planar reflector. The signal model of Madsen et al. (1984) was later extended to backscatter coefficient and attenuation estimation with clinical array transducers by Yao et al. (1990). Yao et al. (1990) accounted for beam diffraction through division of tissue spectra by spectra acquired from a reference phantom with matched sound speed and the same ultrasound system settings.

The reference phantom method developed by Yao et al. (1990) may be considered a spectral difference method. In this method, amplitude changes in the frequency content of the ultrasound pulse are measured over depth and normalized by a reference spectrum from a well-characterized phantom with known attenuation and backscatter. Attenuation is then estimated from the logarithm of the resulting ratio (Yao et al. 1990). Kim and Varghese (2008) later implemented a hybrid method by incorporating the reference phantom method for normalizing spectra to reduce system-dependent effects and then applying a Gaussian filter to the normalized spectra. The frequency shift of the power spectrum with depth was then detected using a cross-correlation algorithm (Kim and Varghese 2008). This algorithm was