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Lower Bound on Estimation Variance of the Ultrasonic Attenuation Coefficient Using the Spectral-Difference Reference Phantom Method

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Abstract

Ultrasonic attenuation is one of the primary parameters of interest in Quantitative Ultrasound (QUS). Non-invasive monitoring of tissue attenuation can provide valuable diagnostic and prognostic information to the physician. The Reference Phantom Method (RPM) was introduced as a way of mitigating some of the system-related effects and biases to facilitate clinical QUS applications. In this paper, under the assumption of diffuse scattering, a probabilistic model of the backscattered signal spectrum is used to derive a theoretical lower bound on the estimation variance of the attenuation coefficient using the Spectral-Difference RPM. The theoretical lower bound is compared to simulated and experimental attenuation estimation statistics in tissue-mimicking (TM) phantoms. Estimation standard deviation (STD) of the sample attenuation in a region of interest (ROI) of the TM phantom is measured for various combinations of processing parameters, including Radio-Frequency (RF) data block length (i.e., window length) from 3 to 17 mm, RF data block width from 10 to 100 A-lines, and number of RF data blocks per attenuation estimation ROI from 3 to 10. In addition to the Spectral-Difference RPM, local attenuation estimation for simulated and experimental data sets was also performed using a modified implementation of the Spectral Fit Method (SFM). Estimation statistics of the SFM are compared to theoretical variance predictions from the literature.¹ Measured STD curves are observed to lie above the theoretical lower bound curves, thus experimentally verifying the validity of the derived bounds. This theoretical framework benefits tissue characterization efforts by isolating processing parameter ranges that could provide required precision levels in estimation of the ultrasonic attenuation coefficient using Spectral Difference methods.

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Keywords

ultrasonic attenuation coefficient; spectral difference; spectral fit; reference phantom method; local estimation; standard deviation

Introduction

Estimation of frequency-dependent ultrasonic attenuation is an important aspect of quantitative ultrasound (QUS) and tissue characterization. It has been studied as a potential classifier of normal and pathological liver tissue,^{2–6} myocardial disease,^{7–9} breast cancers,^{10,11} carotid artery plaques,^{12–14} deep vein thrombosis,^{15,16} osteoporosis,^{17,18} and other tissue types.¹⁹ In addition, accurate attenuation estimation and compensation can lead to improved estimation of other QUS parameters of interest.^{15,16,20–22}

The two major frequency-domain categories of attenuation estimation techniques are spectral shift and spectral difference methods.^{23–25} These frequency-domain methods measure the spectral power density of the echo signals backscattered from different depths within the scattering medium: spectral difference methods estimate the decay of each frequency component with depth and translate it into the ultrasonic attenuation at that frequency. spectral shift methods, however, estimate the apparent shift of the entire power spectrum toward lower frequencies and relate this shift to the ultrasonic attenuation coefficient, that is, the slope of attenuation with frequency; this downshift is due to frequency dependence of attenuation, where high-frequency components of the signal experience higher attenuation than low-frequency components. With either category, there are methods that estimate total path attenuation by analyzing the spectral content from exactly one data block at the depth of interest.^{16,26,27} Separately, there are methods that track spectral changes across many data blocks with depth, within a region of interest (ROI), to estimate attenuation coefficient locally.^{28–30} Other proposed methods estimate attenuation from the time-domain signal.³¹

There are a number of known advantages and disadvantages for each category of attenuation estimation methods that may affect their applicability in a clinical setting. Traditional spectral shift methods, such as the centroid downshift (CDS) method, are susceptible to diffraction effects due to beam focusing and other system-related effects.³² As a result, these methods provide biased estimates outside the focal region of the imaging plane. Spectral difference methods, such as the reference phantom method (RPM)²⁹ and its derivative methods like the spectral log-difference and the spectral fit methods (SFMs), attempt to compensate for diffraction and other system-related effects by including a spectral normalization step. Here, a well-characterized reference phantom with known attenuation and backscatter properties and a similar speed of sound to the biological sample is scanned using exactly the same system settings used for scanning the sample. The power spectrum of the sample is then normalized to that of the reference phantom; effectively cancelling out system-related effects. However, spectral difference methods, like the RPM, suffer from estimation biases due to non-uniformities in the scattering medium such as abrupt backscatter coefficient boundaries, whereas spectral shift methods are not affected as

severely by backscatter-level changes, as long as frequency dependence of backscatter does not drastically change throughout the sample. The hybrid method³³ is a more recent spectral shift estimation technique that includes a spectral normalization step using a reference phantom to compensate for system-related effects. Therefore, it has the most potential for clinical attenuation estimation and imaging where scattering inhomogeneities are commonplace.

Previously, we modeled and analyzed the performance of the CDS method from the spectral shift family of attenuation estimation methods³⁴ and suggested optimizations for implementation of the hybrid method³⁵ that drastically improved its precision and accuracy. In this paper, we apply a similar statistical model of the normalized power spectra to the spectral difference attenuation estimation problem. From this model, we derive the lower bound on variance of all unbiased estimators of the attenuation parameter, otherwise known as the Cramér–Rao lower bound³⁶ (CRLB). We proceed to translate it into a lower bound for the estimation variance of the slope of attenuation with frequency, that is, the attenuation coefficient. To verify our theoretical lower bounds, we process simulated and experimentally acquired phantom radio-frequency (RF) data sets based on two spectral difference methods, that is, the RPM and the SFM. The SFM, a total attenuation estimation method, is implemented with modifications that allow for local estimation of the attenuation coefficient in uniform phantoms. We measure estimation statistics (i.e., mean and variance) of the attenuation coefficient parameter and compare them with our theoretical lower bound. In the case of the SFM, we also compare measurements with corresponding theoretical predictions given by Labyed and Bigelow.¹ Other authors have previously investigated the statistics of scatterer size estimation and provided error bounds based on the Cramér–Rao inequality.^{37,38} However, to the best of our knowledge, such theoretical bounds have not been derived for local estimates of the attenuation coefficient using the spectral difference approach since the early work by Kuc.³⁹

Materials and Methods

Statistical Analysis of the RPM

To estimate ultrasonic attenuation using spectral difference methods, frames of RF data are acquired using the exact same scan settings (i.e., depth, focus, gain, transmit power, etc.) from both a sample and a well-characterized reference phantom. RF data frames are partitioned into blocks consisting of data from several adjacent echo lines that have been windowed at each depth point using a time-gating window function of appropriate length. These windowed data segments are then Fourier transformed, magnitude squared, and averaged to obtain estimates of the signal power spectrum from each block. The power spectrum corresponding to a block at depth z of a homogeneous sample is modeled^{29,33} as

$$S_s(f, z) = S_t(f) D(f, z) BSC_s(f, z) A_s(f, z). \quad (1)$$

In this equation, $S_t(f)$ represents the transmit pulse and transfer functions associated with the boundary between transducer and sample. $D(f, z)$ denotes diffraction effects that are

associated with transducer geometry and beam-forming performed. $BSC_S(f, z)$ is the spectral profile of random scatterers in the sample medium. $A_S(f, z)$ is the cumulative attenuation at frequency f and depth z . Similarly, the power spectrum from a block at depth z of the reference phantom is modeled as

$$S_R(f, z) = S_t(f) D(f, z) BSC_R(f, z) A_R(f, z). \quad (2)$$

Because system settings for both data acquisitions are identical, transmit and diffraction terms are the same in Equations (1) and (2). Therefore, normalizing the sample power spectrum by the reference power spectrum cancels these terms out. The ratio of power spectra is given as

$$RS(f, z) = \frac{S_S(f, z)}{S_R(f, z)} = \frac{BSC_S(f, z) e^{-4\alpha_S(f)z}}{BSC_R(f, z) e^{-4\alpha_R(f)z}} = RB(f, z) e^{-4(\alpha_S(f) - \alpha_R(f))z}. \quad (3)$$

Under diffuse scattering conditions, either with or without the presence of a distributed specular component (i.e., Rician or Rayleigh envelope distribution^{40–42}), the backscatter spectral term from a single periodogram can be modeled as an exponentially distributed random process⁴³ with a probability density function (pdf) given by Equation (4) (Appendix A).

$$p(BSC(f, z)) = \frac{1}{\sigma^2} \exp\left(-\frac{BSC(f, z)}{\sigma^2}\right), \quad BSC(f, z) \geq 0. \quad (4)$$

Therefore, it will have mean $E[BSC(f, z)] = \sigma^2$, and variance $\text{Var}(BSC(f, z)) = \sigma^4$.

If spectra from multiple (N) adjacent A-lines are averaged prior to normalization, the averaged backscatter term will be gamma distributed, with shape and scale parameters as shown in Equation (5).

$$\overline{BSC}(f, z) = \frac{1}{N} \sum_{i=1}^N BSC^{(i)}(f, z) \sim \text{Gamma}\left(N, \frac{\sigma^2}{N}\right). \quad (5)$$

For a sufficiently large N (e.g., N_S and $N_R > 30$), this gamma distribution can be approximated by a normal distribution. Therefore, the averaged backscatter terms for sample and reference power spectra are modeled as

$$\begin{aligned}\overline{BSC}_S(f, z) &\sim \mathcal{N}\left(\sigma_S^2, \frac{\sigma_S^4}{N_S}\right), \\ \overline{BSC}_R(f, z) &\sim \mathcal{N}\left(\sigma_R^2, \frac{\sigma_R^4}{N_R}\right).\end{aligned}\quad (6)$$

Alternatively, a normal distribution of the form given in Equation (6) can be deduced according to the central limit theorem⁴⁴ (CLT) directly and independently from the specific distributions of Equations (4) and (5). However, the mean and the variance would still have to be calculated from the scattering model.

The ratio of the two independent non-zero-mean Gaussian random variables of Equation (6) has a complicated and potentially heavy-tailed distribution without finite moments. However, for large N , it can be shown that sufficient conditions⁴⁵ are met such that this “ BSC ratio random variable,” $RB(f, z)$, is approximately normally distributed about its mean value. We approximate the mean and the variance using a first-order Taylor expansion of the ratio function as given by Equations (7) and (8), respectively.

$$\mu_{RB} = E[RB(f, z)] \approx \frac{E[\overline{BSC}_S(f, z)]}{E[\overline{BSC}_R(f, z)]} = \frac{\sigma_S^2}{\sigma_R^2}, \quad (7)$$

$$\begin{aligned}\sigma_{RB}^2 &= \text{Var}(RB(f, z)) \\ &\approx \frac{E^2[\overline{BSC}_S]}{E^2[\overline{BSC}_R]} \left[\frac{\text{Var}(\overline{BSC}_S)}{E^2[\overline{BSC}_S]} - 2 \frac{\text{Cov}(\overline{BSC}_S, \overline{BSC}_R)}{E[\overline{BSC}_S]E[\overline{BSC}_R]} + \frac{\text{Var}(\overline{BSC}_R)}{E^2[\overline{BSC}_R]} \right] \\ &= \left(\frac{\sigma_S^2}{\sigma_R^2}\right)^2 \left[\frac{1}{N_S} - 0 + \frac{1}{N_R} \right] = \left(\frac{\sigma_S^4}{\sigma_R^4}\right) \frac{N_S + N_R}{N_S N_R}.\end{aligned}\quad (8)$$

Following normalization, the RPM estimates attenuation at each frequency point by performing a least-squares exponential fit on several (L) axially consecutive power spectra. This exponential fit is achieved through a linear regression on the log-spectra from L data blocks. Using the approximation of a normal distribution for $RB(f, z)$, the joint pdf for L consecutive normalized power spectra from L data blocks in the axial direction, denoted by the $\mathbf{L} \times \mathbf{1}$ vector, $RS_L(f, z_0)$, is given in Equation (9). Furthermore, we assume that the statistics of the backscatter term are the same for the L data blocks within this parameter estimation ROI and that the attenuation profile does not change within the ROI. These assumptions are only of concern for non-uniform sample material and are reasonable for small ROI.

$$p(RS_L(f, z_0); \alpha_S(f)) = \prod_{l=0}^{L-1} e^{4(\alpha_S(f) - \alpha_R(f)) \cdot l \Delta z} \cdot \frac{1}{\sqrt{2\pi\sigma_{RB}^2}} \exp \left[-\frac{(RS(f, z_0 + l\Delta z) e^{4(\alpha_S(f) - \alpha_R(f)) \cdot l \Delta z} - \mu_{RB})^2}{2\sigma_{RB}^2} \right]. \quad (9)$$

The sample attenuation is the unknown parameter of this joint pdf that needs to be estimated from the normalized power spectra. Using the joint pdf, the log-likelihood function³⁶ and its first and second derivatives are given in Equations (10), (11), and (12), respectively:

$$\ln(p(RS_L(f, z_0); \alpha_S(f))) = \sum_{l=0}^{L-1} [4(\alpha_S(f) - \alpha_R(f)) \cdot l \Delta z] - \ln \left(\left(2\pi\sigma_{RB}^2 \right)^{L/2} \right) - \frac{1}{2\sigma_{RB}^2} \sum_{l=0}^{L-1} \left(RS(f, z_0 + l\Delta z) e^{4(\alpha_S(f) - \alpha_R(f)) \cdot l \Delta z} - \mu_{RB} \right)^2, \quad (10)$$

$$\frac{\partial}{\partial \alpha_S(f)} \ln(p(RS_L(f, z_0); \alpha_S(f))) = \sum_{l=0}^{L-1} 4l \Delta z - \frac{1}{\sigma_{RB}^2} \sum_{l=0}^{L-1} \left[\begin{aligned} &4l \Delta z RS(f, z_0 + l\Delta z) e^{4(\alpha_S(f) - \alpha_R(f)) \cdot l \Delta z} \\ &\cdot (RS(f, z_0 + l\Delta z) e^{4(\alpha_S(f) - \alpha_R(f)) \cdot l \Delta z} - \mu_{RB}) \end{aligned} \right], \quad (11)$$

$$= -\frac{1}{\sigma_{RB}^2} \sum_{l=0}^{L-1} \left[\begin{aligned} &\frac{\partial^2}{\partial \alpha_S^2(f)} \ln(p(RS_L(f, z_0); \alpha_S(f))) \\ &16l^2 \Delta z^2 RS(f, z_0 + l\Delta z) e^{4(\alpha_S(f) - \alpha_R(f)) \cdot l \Delta z} \\ &(2RS(f, z_0 + l\Delta z) e^{4(\alpha_S(f) - \alpha_R(f)) \cdot l \Delta z} - \mu_{RB}) \end{aligned} \right]. \quad (12)$$

Taking the expected value of Equation (12) gives the Fisher information function³⁶ for the sample attenuation estimate, as written in Equation (13).

$$\begin{aligned} \mathcal{J}(\alpha_S(f)) &= -E \left[\frac{\partial^2}{\partial \alpha_S^2(f)} \ln(p(RS_L(f, z_0); \alpha_S(f))) \mid \alpha_S(f) \right] \\ &= \frac{1}{\sigma_{RB}^2} \sum_{l=0}^{L-1} 16l^2 \Delta z^2 E[RB(f, z_0 + l\Delta z) (2RB(f, z_0 + l\Delta z) - \mu_{RB})] \\ &= \frac{1}{\sigma_{RB}^2} \sum_{l=0}^{L-1} 16l^2 \Delta z^2 \left(2(\mu_{RB}^2 + \sigma_{RB}^2) - \mu_{RB}^2 \right) \\ &= \sum_{l=0}^{L-1} 16l^2 \Delta z^2 \left(\frac{N_S N_R}{N_S + N_R} + 2 \right) \\ &= \frac{8}{3} \Delta z^2 (L-1) L (2L-1) \left(\frac{N_S N_R}{N_S + N_R} + 2 \right). \end{aligned} \quad (13)$$

If N_S and N_R are large, Equation (13) can be approximated with $(8/3) \times z^2 (L-1)L(2L-1)N_S N_R/(N_S + N_R)$. Therefore, we can write the CRLB for the variance of the sample attenuation estimates at each frequency as:

$$\text{Var}(\hat{\alpha}_s(f)) \geq \frac{\frac{N_S + N_R}{N_S N_R}}{\frac{8}{3} \Delta z^2 (L-1)L(2L-1)} \left[\frac{\text{Np}}{\text{cm}} \right]^2. \quad (14)$$

To estimate the attenuation coefficient, the RPM fits the individual attenuation estimates at different frequencies to a linear equation, where the slope of attenuation with frequency gives the attenuation coefficient of the sample in the corresponding ROI. In this linear equation, we model the estimation uncertainties as independent additive zero-mean Gaussian random variables $\varepsilon(f)$, with the same variance σ_α^2 , subject to the CRLB above.

$$\begin{cases} \hat{\alpha}_s(f) = \alpha_0 + \beta_s \cdot f + \varepsilon(f) \\ \varepsilon(f) \sim \mathcal{N}(0, \sigma_\alpha^2) \\ f = m \cdot \Delta f, m = 0, 1, \dots, M-1 \end{cases} \quad (15)$$

This regression is performed over a usable frequency range (M points with a spectral resolution of Δf) where the attenuation estimates are valid, that is, where the power spectrum is above the noise floor. Also, this frequency range can be limited to a range for which the linearity assumption is valid. By taking steps similar to Equations (9) through (14), variance of the maximum likelihood estimator³⁶ of the attenuation coefficient can be written as

$$\begin{aligned} \text{Var}(\hat{\beta}_s) &= \frac{\sigma_\alpha^2}{\frac{1}{6} \Delta f^2 (M-1)M(2M-1)} \\ &\geq \frac{\frac{N_S + N_R}{N_S N_R}}{\frac{4}{9} \Delta f^2 \Delta z^2 (L-1)L(2L-1)(M-1)M(2M-1)}. \end{aligned} \quad (16)$$

If the intercept of the linear relationship α_0 is also assumed to be unknown, a larger variance for the maximum likelihood estimator of the attenuation coefficient is attainable, which leads to the following CRLB for the variance of the attenuation coefficient estimate in Equation (17) (Appendix B).

$$\text{Var}(\hat{\beta}_s) \geq \frac{\frac{N_S + N_R}{N_S N_R}}{\frac{2}{9} \Delta f^2 \Delta z^2 (L-1)L(2L-1)M(M^2-1)} \left[\frac{\text{Np}}{\text{cm} \cdot \text{MHz}} \right]^2. \quad (17)$$

Note that some of these processing parameters are interdependent. For example, data block length determines the frequency resolution and the maximum number of spectral regression points according to Equation (18).

$$\begin{cases} \Delta z = \frac{1}{2} D \cdot c \cdot T_S, \\ \Delta f = \frac{F_S}{D} = \frac{F_S}{\frac{1}{2} \Delta z \cdot F_S} = \frac{c}{2 \Delta z}, \\ M = D \cdot BW\% = \frac{2 \Delta z}{c} \cdot F_S \cdot BW\%, \end{cases} \quad (18)$$

where D represents the total number of RF data points in a windowed segment. Speed of sound is denoted by c . Sampling interval and sampling frequency are shown as T_S and F_S , respectively. Finally, $BW\%$ is the fraction of total bandwidth that is usable for spectral regression. That is, the bandwidth for which the echo signal power spectrum is above the noise floor.

Implementation of the SFM

The SFM is a method for estimation of total attenuation from the transducer surface down to depth z of the imaging plane. This method was introduced and statistically analyzed by Bigelow et al.⁴⁶ Similar to spectral difference methods, the SFM also normalizes the sample power spectrum to the power spectrum of a well-characterized uniformly attenuating tissue-mimicking (TM) phantom. Next, a second-degree polynomial function of frequency is fitted to the normalized power spectra for each ROI. It was shown by Labyed and Bigelow¹ that the coefficient corresponding to the first-degree term is linearly proportional to the attenuation coefficient. Equation (25) of Labyed and Bigelow¹ directly calculates this coefficient from the normalized power spectrum using the method of linear least squares. Equation (26) of the same paper provides a theoretical expression for the estimation variance of this coefficient. We use these same equations to process our simulated and experimental data sets based on the SFM.

To verify the theoretical lower bounds derived above for the spectral difference methods, we compare them with simulated and experimental estimation statistics obtained from both methods, that is, the RPM and the SFM. Another reason for comparing the performance of these two methods is to determine whether there are parameter ranges for which accumulating locally estimated attenuation coefficients by the RPM would give a more robust estimate of the total path attenuation than the one given by the SFM.

To make a meaningful comparison between the two methods, we implement the SFM with some modifications. First, given the a priori information that the TM phantoms are homogeneous and uniformly attenuating, we divide the total attenuation estimated by the SFM for a given data block by the depth of that data block to obtain an estimate of the attenuation coefficient (in [dB/cm/MHz]). Second, because the SFM, unlike the RPM, does not perform an axial regression on the attenuation estimates from adjacent data blocks, we average L axially consecutive estimates to obtain the attenuation coefficient estimate for an ROI that is the same size as the one used with the RPM. Effectively, this step lowers the estimation variance by a factor of L .

Simulated Phantom Study Design

For our simulation study, we created two uniformly attenuating phantoms with attenuation coefficients of 0.7 and 0.5 dB/cm/MHz to serve as sample and reference for the two methods, respectively. These phantoms were created using custom ultrasound simulation software based on classical linear diffraction theory that was developed in our laboratory.⁴⁷ The simulated phantoms were 10 cm deep and 16 cm wide. Scatterers were glass beads with a 50 μ m diameter and density of 10 per cubic millimeter. Speed of sound for the simulated medium was 1540 m/s. These conditions ensure Rayleigh scattering and fully developed speckle. RF data sets consist of 800 independent A-lines, and each A-line was acquired using a simulated linear array transducer with 128 rectangular elements with 0.2-mm spacing, focused at a depth of 40 mm and sampled at 40 MHz.

The simulated phantoms were scanned using a transmit pulse with a Gaussian spectral shape centered at 5.5 MHz with a -3 dB bandwidth of 65%. Additive white Gaussian noise (AWGN) was added to the resulting RF data to simulate electronic system noise. The electronic signal to noise ratio (SNR) was set to 100 dB. Typical range of electronic SNR for clinical scanners is 40 dB or better.

It was suggested in Equations (16) and (17) that the variance of the attenuation coefficient estimates depends on processing parameters such as data block length (z), number of independent A-lines per data block (N_S and N_R), number of axial regression points in an ROI (L), and number of spectral regression points (M). Therefore, we vary these processing parameters as we compare the attenuation coefficient estimated using the two methods (SFM and RPM) and measure corresponding statistics (i.e., mean and standard deviation [STD]) across all the ROIs at the focal depth. The simulated phantoms are wide enough to provide a statistically significant number of estimates for all combinations of processing parameters. These measured statistics are presented in the “Results” section of this paper along with theoretical predictions for the SFM¹ and the theoretical CRLB derived above.

Physical Phantom Study Design

For our experimental data acquisitions, we utilized two uniformly attenuating TM phantoms that were constructed in our laboratory. Both phantoms consist of microscopic glass beads and graphite powder in an agar gel background. The reference phantom has glass beads with diameters ranging from 5 to 43 μ m in concentration of 4 g per liter and a uniform attenuation coefficient of 0.5 dB/cm/MHz ($\pm 2\%$). The sample phantom has glass beads with diameters ranging from 75 to 90 μ m in concentration of 2.8 g per liter, and a uniform attenuation coefficient of 0.8 dB/cm/MHz ($\pm 2\%$). Speed of sound for both phantoms was 1540 m/s.

The physical TM phantoms were scanned using an ACUSON S2000 system (Siemens Medical Solutions USA Inc., Mountain View, California) equipped with a 9L4 linear array transducer. The transmit pulse was centered at 6 MHz with a -3 dB bandwidth of 50%. Imaging depth was set to 6 cm. Focal depth was at 5 cm. Ten independent frames of RF data were collected by translating the transducer in the elevational direction. As in the simulated case, we vary the processing parameters and compute estimation statistics across all

independent frames of RF data. These statistics are plotted against corresponding processing parameters and presented in the “Results” section.

Processing the RF Data

To calculate power spectra from RF data, we divided the sample and reference RF frames into blocks that are of size z along the axial direction and contain $N_S = N_R$ independent A-lines. We multiplied the data segments within each block by a Hann window function. This ensures that the effects of spectral leakage are minimized. Next, we calculated the fast Fourier transform (FFT) of all windowed data segments within a block and averaged the squares of their magnitude to arrive at the power spectrum for that block. The block length, z , is one of the parameters that has a direct impact on the mean and variance of the estimated attenuation coefficient. Comparison of the mean and variance of the attenuation coefficient for the two spectral difference methods were assessed versus this parameter. However, a fixed block length of 10 mm that yielded a stable power spectrum was utilized in other comparisons. Because this is a rather large window size, we utilized a 65% overlap between axially adjacent blocks of data when estimating attenuation. Welch⁴⁸ showed that when using a tapered window such as a Hann or Hamming window function, two adjacent windows with a shift of 50% of the window length are nearly uncorrelated. Our assumption of independence of power spectra from adjacent blocks is valid for large window lengths. However, bias artifacts may be introduced for smaller window lengths, which will be discussed in the “Results” section.

Results

Simulated TM Phantom Results

Number of A-lines per data block—The block length, z , was set to 10 mm, which is equal to eight pulse lengths or 35 wavelengths for this Gaussian transmit pulse. Number of independent A-lines per data block varied from 10 to 100. For received echoes, estimated power spectra had a usable bandwidth from 1.5 to 7.5 MHz. This entire frequency range was used for attenuation estimation with both methods. Axial regression for the RPM was performed using $L = 5$ consecutive data blocks with 65% overlap in each attenuation estimation ROI. Equivalently, five consecutive attenuation estimates of the SFM along the beam direction were averaged to provide the attenuation estimate for a similarly sized ROI. Figure 1 shows the mean attenuation coefficient estimated at the focal depth of the simulated phantom, plotted against the number of A-lines per data block, along with error bars indicating the STD of the estimates. Figure 2 shows the estimation STD measured for each method, along with theoretical prediction of STD for the SFM and the theoretical CRLB derived in this paper. Note that the two methods provide comparable performance, without any significant bias, for the simulated uniform phantoms. The measured STD curves lie above the theoretical CRLB, as expected.

Data block length—To determine an effective block or window length, the number of A-lines per block, N_S and N_R , was set to 30. The number of data blocks per ROI (i.e., the number of axial regression points, L), was set to five for the RPM with 65% overlap between adjacent blocks. Equivalently, five attenuation estimates were averaged per ROI for the

SFM. Block length, z , was varied from 3 to 17 mm as shown in Figure 3, which is equal to 2.5 to 13.5 pulse lengths or 10.5 to 60.5 wavelengths for this Gaussian transmit pulse. Figure 3 shows the mean attenuation coefficient estimated at the focal depth of the simulated phantom plotted against block length. The error bars show STD of the estimates. Estimated STD curves for both methods are plotted in Figure 4 along with theoretical curves. Observe that the RPM suffers from high estimation variance at smaller window lengths. As window length is increased, however, estimation becomes more stable and eventually surpasses the SFM. Once again, the measured STD curves (solid lines) are above the theoretical CRLB curve. However, the theoretical prediction for the SFM starts off below the CRLB curve for smaller window lengths, which suggests those STD values are unobtainable.

Number of data blocks per ROI—To study the effect of changing the number of axial regression points per ROI, we fixed the block length at 10 mm and performed attenuation estimation, at the focal depth of the simulated phantom, using different combinations of number of A-lines per data block and number of data blocks per ROI. The resulting estimation STD curves for $N_S = N_R = 10$ and $N_S = N_R = 50$ are illustrated in Figure 5 along with theoretical CRLB curves associated with the computations. The curves for intermediate values of $N_S = N_R$ fall between these two curves but are not plotted here.

Physical TM Phantom Results

Number of A-lines per data block—Similar to the analysis with simulated phantoms, the block length, z , was set to 10 mm, which is equal to about eight pulse lengths or 35 wavelengths for the corresponding transmit pulse. Number of independent A-lines per data block varied from 10 to 100. For received echoes, estimated power spectra had a usable bandwidth from 2.5 to 7.5 MHz. The entire frequency range was used for attenuation estimation with both methods. Axial regression for RPM was performed using $L = 5$ consecutive data blocks with 65% overlap in each attenuation estimation ROI. Equivalently, five axially consecutive attenuation estimates of the SFM were averaged to provide the attenuation estimate for the same ROI. Figure 6 shows the mean value of the attenuation coefficients estimated across the entire RF frame, plotted against the number of A-lines per data block, along with error bars showing the STD of the estimates. Figure 7 shows the estimation STD measured for each method, along with the theoretical prediction of STD for the SFM and the theoretical CRLB derived above. Note that with the physical TM phantoms, the RPM performs better than the SFM that suffers from increased estimation variance and occasional biased estimation. Also, both experimental curves lie above the theoretical CRLB curve.

Data block length—Here, the number of A-lines per data block, N_S and N_R , were set to 30. The number of data blocks per ROI (i.e., the number of axial regression points, L), was set to five for the RPM using a 65% overlap between adjacent blocks. Equivalently, five attenuation estimates were averaged per ROI for the SFM. Block length, z , was varied from 3 to 17 mm, which is equal to about 2.5 to 13.5 pulse lengths or 10.5 to 60.5 wavelengths for the transmit pulse. Figure 8 shows the mean value of the attenuation coefficients, estimated across the entire RF frame, plotted against block length. The error bars show STD of the estimates. Estimation STD curves for both methods are plotted in Figure 9 along with

theoretical curves. Note that the RPM suffers from high estimation variance and bias at smaller window lengths. As the window length is increased, however, estimation becomes unbiased and more stable and eventually surpasses that obtained using the SFM. As mentioned above, when the blocks are overlapped 65%, the assumption of independence for spectra from axially adjacent blocks is only valid for sufficiently large block lengths and would cause underestimation for small block lengths as seen in Figure 8. Both the measured experimental STD curves are above the CRLB curve. However, theoretical prediction for the SFM starts off below the CRLB curve for small window lengths.

Number of data blocks per ROI—To study the effect of changing the number of axial regression points per ROI, we fixed the data block length at 10 mm and performed attenuation estimation, across the entire frame of RF data acquired from the phantom, for all 10 frames. Analysis was performed using the RPM and with different combinations of number of A-lines per data block and number of data blocks per ROI. The resulting STD curves for $N_S = N_R = 10$ and $N_S = N_R = 50$ are illustrated in Figure 10 along with the associated theoretical CRLB curves. The curves for intermediate values of $N_S = N_R$ fall between these two curves but are not plotted here.

Discussion

It is suggested by the results that estimation performance of the RPM is generally superior to that obtained using the SFM when the data block length is large enough to yield stable power spectral estimates. A possible explanation for the inferior performance of the SFM is that this method estimates the slope of total attenuation in a single step by fitting the logarithm of the normalized power spectrum to a second-degree polynomial function of frequency. This approach involves making two simultaneous assumptions about the sample power spectrum. Namely, linear frequency dependence for attenuation and quadratic frequency dependence for scattering. Imposing such strict modeling restrictions on the normalized power spectrum can degrade the quality of the fit. However, the RPM estimates slope of attenuation in two separate steps without making any assumptions about the power spectrum. Initially, attenuation of each frequency component of the normalized power spectrum with depth is estimated (in dB/cm), and then, these attenuation estimates are fitted to a linear function of frequency to determine the slope of attenuation (in dB/cm/MHz).

In addition, it appears that estimation of total attenuation down to depth Z by means of accumulating local attenuation estimates almost always outperformed direct estimation of total attenuation using the SFM in this study. The only exception appears to be when sample size limitations prohibit the use of sufficiently large data blocks. In these cases, the RPM provides biased estimates with higher variance compared with the SFM as is illustrated in Figure 8. The reason for this contrast in performance is the fact that the SFM only uses the spectral information from one block at depth Z and discards the information contained in the preceding $K - 1$ data blocks, whereas accumulating local attenuation estimates creates a weighted sum of these spectral estimates that lowers the total estimation variance by a factor of K , as seen in Equation (19) below.

$$\begin{cases} \text{Var} \left(Att_{\text{SFM}}^{\text{total}}(Z) \right) = \text{Var} \left(Z \cdot \hat{\beta}_{\text{SFM}}(Z) \right) = Z^2 \cdot \text{Var} \left(\hat{\beta}_{\text{SFM}} \right), \\ \text{Var} \left(Att_{\text{RPM}}^{\text{total}}(Z) \right) = \text{Var} \left(\sum_{i=1}^K \Delta z \cdot \hat{\beta}_{\text{RPM}}(i\Delta z) \right) = K \cdot \Delta z^2 \cdot \text{Var} \left(\hat{\beta}_{\text{RPM}} \right) = \frac{Z^2}{K} \cdot \text{Var} \left(\hat{\beta}_{\text{RPM}} \right). \end{cases}$$

(19)

It is worth noting that the derived theoretical lower bounds (CRLB) in this paper are about three to four times smaller than the estimation precision that is observed from the RPM in our simulated and experimental phantom studies. A similar finding was reported by Chaturvedi et al.³⁷ for the CRLB on scatterer size estimates. This suggests that the derived theoretical lower bound, although valid, may not be the optimal bound for gauging the performance of the RPM. There are two possible sources for the observed discrepancy. One is the basic model of Equation (4) that was used to derive the mean and variance of Equations (7) and (8) and eventually develop the joint pdf of Equation (9) and CRLB of Equation (14). A more detailed model of the backscatter coefficient may provide a larger, more realistic lower bound for the frequency-dependent attenuation estimate, $\hat{\alpha}_s(f)$. The second possible source of underestimation is the assumption of white (i.e., uncorrelated) estimation errors, $\epsilon(f)$, in the linear regression step of Equation (15). A correlated error vector with a covariance matrix that has nonzero values off the diagonal will result in higher variability in the estimates of the attenuation coefficient, β_s . Therefore, the lower bounds of Equations (16) and (17) may be too optimistic in such cases. Analysis on the estimates from our simulated study revealed the existence of some correlation between the estimates separated by one frequency resolution unit, Δf . This discussion points toward future works involving more complicated modeling such as an autoregressive (AR) model of the frequency-dependent attenuation estimates and generalized least-squares regression.

Conclusion

We have derived a theoretical lower bound (CRLB) on the variance of attenuation coefficients estimated using the spectral difference RPM in terms of processing parameters such as window size, number of A-lines per data block, number of data blocks per estimation ROI, and usable spectral bandwidth. We experimentally verified our theoretical lower bound by comparing it with estimation statistics from both simulated and physical TM phantom scans using two separate attenuation estimation methods.

This theoretical framework can benefit tissue characterization efforts by isolating processing parameter ranges (e.g., gating window length, data block width, number of data blocks per ROI, analysis bandwidth, etc.) that should be investigated for achieving required levels of precision in attenuation estimation and by rejecting parameter ranges that would not provide such requirements (e.g., theoretical curve of Figure 9 suggests that an estimation precision of 0.1 dB/cm/MHz or better is not achievable for window lengths smaller than 4 mm).

Future work will include more detailed modeling as well as modifications to the spectral-difference attenuation estimator that should bring the observed performance and the theoretical bound closer together.

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Appendix A

Power Spectral Distribution

If the number of scatterers within the resolution cell contributing to the complex field is large, the analytic signal corresponding to an N_x -point segment of an RF A-line, that we denote with $x[n]$, constitutes a complex-valued stationary random process that is circularly Gaussian and white. It may have a non-zero complex mean μ and variance σ_x^2 such that we can decompose it into a constant and a zero-mean part:

$$x[n] = \mu + \tilde{x}[n]. \quad (\text{A1})$$

The real and imaginary parts of $\tilde{x}[n]$, denoted by $\tilde{x}_r[n]$ and $\tilde{x}_i[n]$, are independent and identically distributed Gaussian random processes with equal variances $\sigma_x^2/2$. Therefore, the joint probability density function (pdf) of $x_r[n]$ and $x_i[n]$ will be given by Equation (A2).

$$p_{x_r x_i}(x_r, x_i) = \frac{1}{\pi \sigma_x^2} \exp \left(-\frac{1}{\sigma_x^2} \left[(x_r - \mu_r)^2 + (x_i - \mu_i)^2 \right] \right). \quad (\text{A2})$$

The pdf of the envelope $|x[n]|$ can then be shown (Papoulis et al.⁴⁴) to have a Rician distribution given by Equation (A3).

$$p_{|x|}(|x|) = \frac{2|x|}{\sigma_x^2} \exp \left[-\frac{1}{\sigma_x^2} (|x|^2 + |\mu|^2) \right] I_0 \left(\frac{2|x||\mu|}{\sigma_x^2} \right), |x| \geq 0, \quad (\text{A3})$$

where $I_0(\cdot)$ is the modified Bessel function of the first kind and zero order. In the special zero-mean case, the pdf above reduces to a Rayleigh distribution.

Assuming an N_x -point window function $w[n]$, we can write the joint pdf for the real and imaginary parts of the discrete-time Fourier transform (DTFT) of a windowed $x_w[n]$ as shown in Equation (A4).

$$p_{X_{wr} X_{wi}}(X_{wr}, X_{wi}) = \frac{1}{\pi E_w \sigma_x^2} \exp \left(-\frac{1}{E_w \sigma_x^2} [(X_{wr} - \gamma_r)^2 + (X_{wi} - \gamma_i)^2] \right), \quad (\text{A4})$$

where E_w denotes the energy of the window function and γ is the product of the signal mean μ and the DTFT of the window function $W(\omega)$. When a rectangular window function is used, E_w will simply be equal to N_x , and $W(\omega)$ will be the aliased sinc function.

Similar to Equation (A3), the pdf for $|X(\omega)|$ will have a Rician distribution as given in Equation (A5).

$$p_{|X|}(|X|) = \frac{2|X|}{E_w \sigma_x^2} \exp \left[-\frac{1}{E_w \sigma_x^2} (|X|^2 + |\gamma|^2) \right] I_0 \left(\frac{2|X||\gamma|}{E_w \sigma_x^2} \right), |X| \geq 0. \quad (\text{A5})$$

Finally, the pdf for the magnitude squared of the signal DTFT $Y = |X|^2$ at a particular frequency can be shown (Papoulis et al.⁴⁴) to have a pdf as shown in Equation (A6), which implies a non-central chi-square distribution in $2Y/(E_w \sigma_x^2)$.

$$p_Y(Y) = \frac{1}{E_w \sigma_x^2} \exp \left[-\frac{1}{E_w \sigma_x^2} (Y + |\gamma|^2) \right] I_0 \left(\frac{2\sqrt{Y}|\gamma|}{E_w \sigma_x^2} \right), Y \geq 0. \quad (\text{A6})$$

To simplify Equation (A6) further, assume a rectangular window function. When using a FFT to calculate the N_x -point discrete Fourier transform (DFT), the only non-zero value of $\gamma[k]$ will be at the DC frequency $k=0$ and the zeros of the aliased sinc function will coincide with all other frequency bins. Therefore, at these frequencies, the pdf of the power spectrum will reduce to Equation (A7). Same result can be drawn at all frequencies if the process is zero-mean, that is, fully developed speckle. Thus, the exponential distribution with a single parameter $\sigma^2 = N_x \sigma_x^2$ representing the backscattered intensity from the random medium,⁴³ is selected for the power spectral model presented in this paper.

$$p_Y(Y) = \frac{1}{N_x \sigma_x^2} \exp \left[-\frac{Y}{N_x \sigma_x^2} \right], Y \geq 0. \quad (\text{A7})$$

Appendix B

Line Fitting with Two Unknown Coefficients

Consider the line fitting problem from the “Materials and Methods” section again,

$$\begin{cases} \hat{\alpha}_S(f) = \alpha_0 + \beta_S \cdot f + \varepsilon(f) \\ \varepsilon(f) \sim \mathcal{N}(0, \sigma_\alpha^2) \\ f = m \cdot \Delta f, m = 0, 1, \dots, M-1 \end{cases} \quad (\text{B1})$$

We are interested in estimating α_0 and β_S simultaneously. The matrix form of the problem can be written as $\hat{\alpha}_S = H\theta + \varepsilon$ with the terms defined in Equation (B2).

$$\hat{\alpha}_S = \begin{bmatrix} \hat{\alpha}_S(0) \\ \vdots \\ \hat{\alpha}_S((M-1) \cdot \Delta f) \end{bmatrix}, H \triangleq \begin{bmatrix} 1 & 0 \\ 1 & \Delta f \\ \vdots & \vdots \\ 1 & (M-1) \cdot \Delta f \end{bmatrix}, \theta = \begin{bmatrix} \alpha_0 \\ \beta_S \end{bmatrix}, \varepsilon = \begin{bmatrix} \varepsilon(0) \\ \vdots \\ \varepsilon((M-1) \cdot \Delta f) \end{bmatrix}. \quad (\text{B2})$$

Similar to the derivations in the paper, the score function³⁶ and the Fisher information function can be written as shown in Equation (B3).

$$\frac{\partial \ln p(\hat{\alpha}_S; \theta)}{\partial \theta} = \left[H^T \hat{\alpha}_S - H^T H \theta \right] / \sigma_\alpha^2, \\ I(\theta) = \frac{H^T H}{\sigma_\alpha^2} = \begin{bmatrix} \frac{M}{\sigma_\alpha^2} & \frac{M(M-1)\Delta f}{2\sigma_\alpha^2} \\ \frac{M(M-1)\Delta f}{2\sigma_\alpha^2} & \frac{M(M-1)(2M-1)\Delta f^2}{6\sigma_\alpha^2} \end{bmatrix}. \quad (\text{B3})$$

Therefore, the score function can be restructured as the canonical form given in Equation (B4) that gives the minimum-variance unbiased (MVU) estimator,³⁶ and the inverse of $I(\theta)$ gives the covariance matrix for the estimates.

$$\frac{\partial \ln p(\hat{\alpha}_S; \theta)}{\partial \theta} = I(\theta) \left[\left(H^T H \right)^{-1} H^T \hat{\alpha}_S - \theta \right] = I(\theta) \left[\hat{\theta} - \theta \right],$$

$$I^{-1}(\theta) = \begin{bmatrix} \frac{2(2M-1)\sigma_\alpha^2}{M(M+1)} & -\frac{6\sigma_\alpha^2}{M(M+1)\Delta f} \\ -\frac{6\sigma_\alpha^2}{M(M+1)\Delta f} & \frac{12\sigma_\alpha^2}{M(M^2-1)\Delta f^2} \end{bmatrix}. \quad (\text{B4})$$

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Figure 1.

Mean attenuation coefficient at the focal depth of the simulated uniform TM phantom estimated using the RPM (red) and the SFM (blue) plotted against the number of independent A-lines per data block ($N_S = N_R = 10:5:100$). Other parameter settings: $z = 10\text{mm}$, $L = 5$, and usable bandwidth from 1.5 to 7.5 MHz. Both methods perform similarly without any significant bias in their estimates. TM = tissue-mimicking; RPM = reference phantom method; SFM = spectral fit method.

Figure 2.

Estimation standard deviation for attenuation coefficient at focal depth of the simulated uniform TM phantom estimated using the RPM and the SFM plotted against the number of independent A-lines per data block ($N_S = N_R = 10:5:100$). Other parameter settings: $z = 10\text{mm}$, $L = 5$, and usable bandwidth from 1.5 to 7.5 MHz. Both methods perform similarly without any significant bias in their estimates. Dashed lines show the theoretical lower bound for the RPM that was derived in this paper and the theoretical prediction for the SFM as provided in Labyed and Bigelow.¹ Measurements lie above the theoretical bounds. TM = tissue-mimicking; RPM = reference phantom method; SFM = spectral fit method; CRLB = Cramér–Rao lower bound.

Figure 3.

Mean attenuation at the focal depth of the simulated uniform TM phantom estimated using the RPM (red) and the SFM (blue) plotted against data block length ($z = 3:1:17$ mm). Other parameter settings: $N_S = N_R = 30$, $L = 5$, and usable bandwidth from 1.5 to 7.5 MHz. Both methods perform similarly without any significant bias in their estimates. Both methods show negligible bias. However, RPM estimates initially have higher variance for small data blocks. TM = tissue-mimicking; RPM = reference phantom method; SFM = spectral fit method.

Figure 4.

Estimation standard deviation for attenuation coefficient at focal depth of the simulated uniform TM phantom estimated using the RPM and the SFM plotted against data block length ($\Delta z = 3:17$ mm). Other parameter settings: $N_S = N_R = 30$, $L = 5$, and usable bandwidth from 1.5 to 7.5 MHz. Dashed lines show the theoretical lower bound for the RPM that was derived in this paper and the theoretical prediction for the SFM as provided in Labyed and Bigelow.¹ Measurements lie above the theoretical bounds. TM = tissue-mimicking; RPM = reference phantom method; SFM = spectral fit method; CRLB = Cramér–Rao lower bound.

Figure 5.

Estimation standard deviation for attenuation coefficient at the focal depth of the simulated uniform TM phantom estimated using the RPM plotted against the number of data blocks per parameter estimation ROI ($L = 3:1:10$). Other parameter settings: $z = 10\text{mm}$ and usable bandwidth from 1.5 to 7.5 MHz. Dashed lines show the theoretical lower bound for the RPM that was derived in this paper. Measurements lie above the theoretical bounds. TM = tissue-mimicking; RPM = reference phantom method; ROI = region of interest; CRLB = Cramér–Rao lower bound.

Figure 6.

Mean attenuation coefficient of the physical uniform TM phantom estimated using the RPM (red) and the SFM (blue) plotted against the number of independent A-lines per data block ($N_S = N_R = 10:5:100$). Other parameter settings: $z = 10\text{mm}$, $L = 5$, and usable bandwidth from 2.5 to 7.5 MHz. The RPM outperforms the SFM that suffers from some bias and higher estimation variance. TM = tissue-mimicking; RPM = reference phantom method; SFM = spectral fit method.

Figure 7.

Estimation standard deviation for attenuation coefficient of the physical uniform TM phantom estimated using the RPM and the SFM plotted against the number of independent A-lines per data block ($N_S = N_R = 10:5:100$). Other parameter settings: $z = 10\text{mm}$, $L = 5$, and usable bandwidth from 2.5 to 7.5 MHz. Dashed lines show the theoretical lower bound for the RPM that was derived in this paper and the theoretical prediction for the SFM as provided in Labyed and Bigelow.¹ Measurements lie above the theoretical bounds. TM = tissue-mimicking; RPM = reference phantom method; SFM = spectral fit method; CRLB = Cramér–Rao lower bound.

Figure 8.

Mean attenuation of the physical uniform TM phantom estimated using the RPM (red) and the SFM (blue) plotted against data block length ($\Delta z = 3:1:17$ mm). Other parameter settings: $N_S = N_R = 30$, $L = 5$, and usable bandwidth from 2.5 to 7.5 MHz. The SFM shows no significant bias. The RPM initially underestimates the attenuation and has higher estimation variance for small data blocks. However, for larger data blocks, the RPM outperforms the SFM. TM = tissue-mimicking; RPM = reference phantom method; SFM = spectral fit method.

Figure 9.

Estimation standard deviation for attenuation coefficient of the physical uniform TM phantom estimated using the RPM and the SFM plotted against data block length ($\Delta z = 3:1:17$ mm). Other parameter settings: $N_S = N_R = 30$, $L = 5$, and usable bandwidth from 2.5 to 7.5 MHz. Dashed lines show the theoretical lower bound for the RPM that was derived in this paper and the theoretical prediction for the SFM as provided in Labyed and Bigelow.¹ Experimental measurements lie above the theoretical bounds. TM = tissue-mimicking; RPM = reference phantom method; SFM = spectral fit method; CRLB = Cramér–Rao lower bound.

Figure 10.

Estimation standard deviation for attenuation coefficient of the physical uniform TM phantom estimated using the RPM plotted against the number of data blocks per parameter estimation ROI ($L = 3:1:10$). Other parameter settings: $z = 10\text{mm}$ and usable bandwidth from 2.5 to 7.5 MHz. Dashed lines show the theoretical lower bound for the RPM that was derived in this paper. Experimental measurements lie above the theoretical bounds. TM = tissue-mimicking; RPM = reference phantom method; ROI = region of interest; CRLB = Cramér–Rao lower bound.