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A Quantitative Ultrasound-Based Multi-Parameter Classifier for Breast Masses

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Abstract

This manuscript reports preliminary results obtained by combining estimates of two or three (among seven) quantitative ultrasound (QUS) parameters in a model-free, multi-parameter classifier to differentiate breast carcinomas from fibroadenomas (the most common benign solid tumor). Forty-three subjects scheduled for core biopsy of a suspicious breast mass were recruited. Radiofrequency echo signal data were acquired using clinical breast ultrasound systems equipped with linear array transducers. The Reference Phantom Method was used to obtain system-independent estimates of the specific attenuation (ATT), the average backscatter coefficients (ABSC), the effective scatterer diameter (ESD) and an effective scatterer diameter heterogeneity index (ESDHI) over regions of interest within each mass. In addition, the envelope amplitude signal-to-noise ratio (SNR), the Nakagami shape parameter, m , and the maximum collapsed average (maxCA) of the generalized spectrum were also computed. Classification was performed using the minimum Mahalanobis distance to the centroids of the training classes and tested against biopsy results. Classification performance was evaluated with the area under the receiver-operating characteristic (ROC) curve. The best performance with a two-parameter classifier used the ESD and ESDHI and resulted in an area under the ROC curve of 0.98 [0.95–1.00, 95% confidence interval]. Classification performance improved with three parameters (ATT, ESD, and ESDHI) yielding an area under the ROC curve of 0.999 [0.995–1.000]. These results suggest that system independent QUS parameters, when combined in a model-free classifier, are a promising tool to characterize breast tumors. A larger study is needed to further test this idea.

Keywords

Mahalanobis classifier; attenuation; backscatter coefficient; effective scatterer diameter; heterogeneity index; quantitative ultrasound

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Introduction

Distinguishing benign from malignant breast masses by way of imaging tests continues to be an important medical challenge. Breast cancer is the second most common cancer among women and the second leading cause of cancer deaths in women in the United States (Siegel et al., 2017). The American Cancer Society (2017) recommends annual mammograms for women age 45 and over with average risk of breast cancer.

Ultrasound plays an important role in breast cancer diagnosis. The modality has become a valuable diagnostic tool used in conjunction with mammography because the equipment is widely available, is cost-effective, and provides unique soft tissue information. Ultrasound is effective even in dense breasts, where mammography has a low sensitivity. Berg et al. (2012) studied breast examination results for 2662 women, among which there were 4814 incidence screens (annual screens for second and third years of study). In that group, the authors observed sensitivity and specificity for mammography alone of about 0.52 and 0.91, respectively. When ultrasound was included, the sensitivity for both modalities together increased to 0.76, but the specificity decreased to 0.84. When magnetic resonance imaging (MRI) was included with mammography plus ultrasound, the sensitivity increased to 1.0, but the specificity decreased to 0.65. Clearly, improvements in the specificity of breast ultrasound could have a significant impact on image-based breast mass classification.

Quantitative ultrasound (QUS) methods enable accurate, clinically-based estimates of acoustic properties of tissues by accounting for instrumentation and wave propagation dependencies that affect pulse-echo data (Anderson et al., 2010; Nam et al., 2012). QUS characterization of tissues is generally based on the premise that disease processes modify the acoustic properties of tissue and that observer- and system-independent parameter estimates can enhance the overall diagnostic accuracy of the modality.

Commonly estimated acoustic properties are the attenuation coefficient, which quantifies the spatial rate at which an ultrasound beam loses energy while traversing a particular tissue, and the backscatter coefficient (BSC), which quantifies the fraction of the ultrasound energy that returns to the transducer per unit volume of scatterers (D'Astous and Foster, 1986). The attenuation coefficient is often reported in terms of the specific attenuation (ATT) (International Electrotechnical Commission, 2010), which is the slope of the attenuation coefficient vs. frequency at a given frequency. The BSC is parametrized in terms of the frequency average BSC (ABSC), which quantifies echogenicity (Nam et al., 2013), and the effective scatterer diameter, ESD, which encodes the frequency-dependence of backscatter and describes the spatial correlation function of echo signal sources.

Attenuation and backscatter coefficients were investigated by D'Astous and Foster (1986) to characterize *ex vivo* breast tissue samples. The authors found that the attenuation coefficient and its dependence on frequency between 3 and 8 MHz were different among infiltrating ductal cancer (IDC), breast parenchyma, and fat. They also found differences among these tissues in the magnitude and frequency-dependence of the BSC. Further, they demonstrated that a 2-parameter analysis (attenuation and BSC) was sufficient to separate the 3 distinct tissue types they studied. Mortensen et al. (1996) used an artificial neural network and a

feature set consisting of sound speed, attenuation and backscatter parameters to differentiate *ex vivo* breast tissue samples as either 'normal', 'benign', or 'malignant'. They achieved 0.93 accuracy, far exceeding the 0.729 found by Stavros et al. (1995) for standard clinical sonography, even though their data acquisition system did not provide image guidance for region of interest (ROI) selection. Tadayyon et al. (2014) and Sannachi et al. (2015) also demonstrated the potential of QUS for evaluation of locally advanced breast cancers. Using a set of QUS parameters, they were able to differentiate between histologic Grade I versus Grades II and III tumors with an accuracy of 0.86, and their QUS parameters could provide early measures of tumor response to neoadjuvant chemotherapy in as little as one week after treatment began. Other investigators have implemented different approaches to breast QUS that do not provide system-independent results. For example, Garra et al. (1993) digitized the video output of an ultrasound scanner and analyzed the statistics of the B-mode image texture of breast scans. Although their patient population was small, they used low frequency (5 and 7.5 MHz) transducers, and they had comparatively poor-quality data, they were able to correctly identify 78% of the fibroadenomas, 73% of the cysts, and 91% of the fibrocystic nodules while maintaining high sensitivity for cancer for this patient group. Using similar data acquisition, image texture parameters and an artificial neural network, Chen and Hsiao (2008) obtained a diagnostic accuracy of 95%. Their success demonstrated that measures of texture statistics have merit for differentiating among breast diseases. Texture statistics vary because of variations in frequency-dependent scattering as well as system-dependent functions. Thus, the success of these techniques will likely carry over to system-independent breast QUS techniques.

System-independent QUS parameters can be obtained through the Reference Phantom Method proposed by our group (Yao et al., 1990). This method has been tested in multiple studies using different imaging systems, and has consistently demonstrated system-independent estimates in excellent agreement with theory and independent measurements (Nam et al., 2011a,b, 2012; Rosado-Mendez et al., 2013; Wirtzfeld et al., 2013). We have recently improved this approach in various ways to increase its accuracy and precision. Rosado-Mendez et al. (2013) demonstrated that the multitaper estimator of the echo signal power spectrum reduced the variance of attenuation estimates. Nam et al. (2011b) developed a method to compensate for the attenuation of intervening tissues in the estimation of the backscatter coefficient, which was further refined by Nasief et al. (2015) to consider power-law frequency-dependent attenuation. Application of these improvements to breast imaging allowed us to demonstrate correlation of QUS parameters with physically homologous visual features described using the BIRADS system. For example, Nam et al. (2013) demonstrated that estimates of the product of the acoustic attenuation coefficient and the lesion size (along the acoustic beam direction) correlated well with the assessment of the ultrasound BI-RADS descriptor 'posterior acoustic features'. We also studied QUS parameters to characterize breast fat *in vivo* (Nasief et al., 2015). We found consistency in attenuation estimates among 24 subjects. Moreover, the ABSC for breast fat was within a 5 dB range among all subjects, supporting the notion that breast fat is a reasonable tissue for subjective comparisons. These results agree with the common use of breast fat as a visual reference to assess echogenicity of suspicious masses. Taken together, these studies support the use of QUS parameters as quantitative surrogates of visual features of breast ultrasound

images with the possibility of improving the diagnostic performance of ultrasound through classification techniques.

Various statistical and machine learning classification strategies have been explored in the context of breast ultrasound. Algorithms and analysis tools utilizing a Bayesian classifier have been developed that combine parameter estimates to differentiate cancer types and predict their recurrence based on mammography data, (Burnside et al., 2006; Kahn et al., 1997; Dumitru, 2009; Gadewadikar et al., 2010) but none have been reported using QUS. One of the challenges with using Bayesian classifiers is that the computational complexity of these networks increases as the number of parameters involved increases. More recently, Tadayyon et al. (2014) compared the performance of Fisher's linear discriminant, k nearest neighbor and support vector machine classifiers fed with QUS parameters and texture features from QUS parametric images of breast masses to identify good respondents to neoadjuvant chemotherapy of breast masses. They were able to differentiate these from poor and non-respondents with an accuracy of 88%. However, many of these classification methods are limited by the need to fulfill assumptions regarding data statistical distributions. Alternatively, a data-driven classifier based on the Mahalanobis distance frees the user from the need to demonstrate compliance with these assumptions.

This paper describes a Mahalanobis-distance classifier to differentiate between fibroadenomas and carcinomas utilizing QUS parameters obtained from improved signal processing methods. Use of this classifier readily illustrated the potential of specific combinations of QUS parameters to classify a mass as malignant or non-malignant. A brief description of each parameter is provided. Encouraging initial test results are reported; limitations of the study are also considered.

Materials and Methods

One-hundred-twenty women scheduled for ultrasound-guided biopsy of previously detected breast tumors were recruited following a University of Wisconsin Institutional Review Board-approved, Health Insurance Portability and Accountability Act-compliant protocol. These patients typically have had screening and diagnostic mammograms and have a lesion sufficiently suspicious to warrant biopsy. The inclusion criteria considered age of at least 18 years to provide informed consent and lesion size larger than 5mm in the axial dimension and less than 20 mm in the major dimension (half the width of the typical ultrasound field of view). The minimum lesion size restriction was imposed to limit bias and variance in attenuation estimates (Rosado-Mendez et al., 2013). The maximum lesion size restriction was set so that the echogenicity of the lesion on the B mode image could be compared at the same depth with that of the surrounding tissue. Due to limited sample size, we restricted the analysis to breast masses diagnosed by core biopsy as carcinoma or fibroadenoma (the most common benign solid lesions) which is a clinically relevant distinction for diagnosis (American Cancer Society, 2019a,b).

There were two subgroups of subjects. Fifty-one subjects were scanned using a custom elasticity imaging mode on a Siemens Antares (Siemens Medical Solutions USA, Inc., Malvern, PA, USA) equipped with a VFX13-5 linear array transducer (9 MHz nominal

frequency). Radiofrequency (RF) echo signal data were recorded while the sonographer applied small deformations using the transducer, with an interframe axial strain of less than 1%. Each frame consisted of either 256 or 312 acoustic scan lines. For QUS analysis, we used the initial RF echo signal frame (before compression).

Echo signals also were recorded from a reference phantom using the same transducer and system settings. The reference phantom background material was a 70% safflower oil-gelatin emulsion (Madsen et al., 2006). The acoustic attenuation in the phantom was $0.54 \text{ dB}\cdot\text{cm}^{-1}\text{MHz}^{-1}$, the speed of sound was 1492 m/s, and the backscatter coefficient was $0.36\times 10^{-2} \text{ cm}^{-1}\text{sr}^{-1}$ at 7 MHz. These were measured using laboratory apparatus applied to test cylinders manufactured with the phantom (Madsen et al., 1999).

The second subgroup included sixty-nine subjects scanned in the supine position and in the radial plane (image plane aligned with ducts). Data were acquired using a Siemens S2000 system (Siemens Medical Solutions USA, Inc., Malvern, PA, USA) with an 18L6 linear array transducer (10 MHz nominal frequency). The system was equipped with the Axis Direct Ultrasound Research Interface (Brunke et al., 2007) that allowed acquisition of beamformed RF echo signals following time-gain compensation but before envelope detection and post-processing. Beams were steered to acquire RF data from -10° to $+10^\circ$ (counterclockwise, with respect to the axis perpendicular to the transducer aperture), in 5° steps. Similar to the first patient group, an equivalent reference phantom was scanned immediately after the patient images and data were acquired, using the same transducer and system settings. To characterize the transducer spatial response, the axial and lateral pulse-echo correlation lengths were estimated using methods described by Thijssen (2003), i.e., computing echo signal correlations axially as well as between adjacent (lateral) acoustic scan line signals. In the axial direction, we define the “pulse-echo correlation length” as the full width of the two-sided correlation curve at a value of 0.2, i.e., twice the one-sided axial correlation length. When scanning with the 18L6 transducer at a nominal setting of 10 MHz for the 0° scan those were 0.26 mm and four adjacent acoustic scan lines, respectively. There were no significant differences in the axial or lateral correlation lengths when beams were steered $\pm 5^\circ$. These results suggest that data from small steering angles can be utilized to obtain additional independent samples of the echo signals, when needed, for small tumors (Gerig et al., 2004) (see below).

Data sets with poor quality reference phantom data (insufficient electronic SNR to meet the 4–9 MHz bandwidth criterion (see first paragraph of next section) or presence of artifacts from reverberations, etc.) were excluded. This resulted in data from 43 subjects including 27 fibroadenomas, 10 invasive (or infiltrating) ductal carcinomas, 2 invasive lobular carcinomas, 1 adenocarcinoma, 1 intracystic papillary carcinoma, and 2 ductal carcinomas *in situ*.

QUS Parameter Estimation

Once the echo signal data were acquired, offline analysis was performed using MATLAB (Mathworks, Natick, MA, USA) to estimate QUS parameters. Power spectra were estimated within a selected region of interest (ROI) using a multitaper method (Percival and Walden, 1993; Rosado-Mendez et al., 2013) with a time-half bandwidth product (NW) of 4, and 4×4

mm² power spectrum estimation regions (PSER) overlapping by 90% both axially and laterally (Nam et al., 2011a,b; Wirtzfeld et al., 2013). For tumors smaller than 6 mm in the axial direction, 3×3 mm² power spectrum estimation regions were used. To compensate for the increase in power spectrum variance associated with smaller windows, power spectra from uncorrelated echo signals from beams steered ±5 degrees were included to improve the statistics of average power spectral estimates (Gerig et al., 2004; Liu and Zagzebski, 2010). An analysis bandwidth of 4–9 MHz, corresponding to power spectral densities at least 10 dB above the noise floor, was used in estimations of attenuation and backscatter coefficients. The ROI size was (by subjective B-mode image assessment) the largest homogeneous region within the tumor boundary outlined by the sonographer at the time of the scan. Pathology identification of tumor type was based on core biopsy specimens.

Attenuation and backscatter coefficients within the tumor were estimated using the reference phantom method (RPM) (Yao et al., 1990). The RPM utilizes the ratio of the echo signal power spectra from the tissue to the power spectra from the same depth in the reference phantom. This can be modeled as:

$$\frac{S_s(f, z)}{S_r(f, z)} = \frac{BSC_s(f, z)}{BSC_r(f, z)} \exp(-4(\alpha_{\text{eff},s}(f) - \alpha_r(f))z) \quad (1)$$

where $S(f, z)$ represents the power spectra, subscripts s and r refer to the sample and reference, BSC_s is the backscatter coefficient of the sample, α_r is the reference attenuation coefficient, f is the frequency and z is the depth. $\alpha_{\text{eff},s}$ is the effective attenuation in the sample (the average of the sample attenuation coefficient $\alpha_s(f, z)$ considering all intervening tissues) down to a depth z .

$$\alpha_{\text{eff},s}(f) = \frac{1}{z} \int_0^z \alpha_s(f, z') dz' \quad (2)$$

Estimates of the attenuation coefficient and the backscatter coefficient in the lesion were obtained from Equation 1 as described below.

Specific attenuation ATT

This parameter was estimated from the local attenuation coefficient $\alpha_{L,s}(f, z)$, i.e., the attenuation coefficient of the tissue within a single parameter estimation region (PER) centered at depth z within the ROI (Fig. 1). Assuming that α_s and BSC_s are constant within the PER, $\alpha_{L,s}(f, z)$ is obtained by quantifying the local rate of change of the power spectrum ratio as a function of depth at each frequency (Zagzebski et al., 1993). ATT estimates the power loss as a function of depth among a sequence of PSERs in a single PER. It is obtained from the slope of a linear fit to the local attenuation vs. frequency, i.e., $\alpha_{L,s}(f) = \text{ATT} \times f$ (Nam et al., 2013).

Backscatter coefficient BSC

The backscatter coefficient estimation was performed on each PSER. The estimation of BSC from Eq. 1 requires knowledge of the intervening tissue effective attenuation $\alpha_{\text{eff},s}$. Taking the natural logarithm of the ratio of the power spectra in Eq. 1, and modeling the attenuation

and backscatter coefficients as linear ($\alpha(f) = \alpha_0 f$) and power law ($BSC(f) = bf^m$) functions of frequency, respectively, we obtain

$$\ln \frac{S_s(f, z)}{S_r(f, z)} = \ln \frac{b_s}{b_r} + (n_s - n_r) \ln f - 4(\alpha_{o, \text{eff}, s} - \alpha_{o, r}) f z \quad (3)$$

A least-squares linear fit (Nasief et al., 2015) was used to solve for the unknowns, b_s , n_s and $\alpha_{o, \text{eff}, s}$ in Eq. 3 that were consistent with the power spectrum data within the frequency band. This was done for frequency intervals of 2 MHz so that the linear dependence of attenuation on frequency assumed in Eq. 3 is a reasonable approximation. The entire 4–9 MHz bandwidth was covered by repeating this process at successive 2 MHz intervals, overlapping by 50%. The resultant values of $\alpha_{o, \text{eff}, s}$ generated for individual frequency intervals were combined using a power law fit to describe the frequency dependence of $\alpha_{\text{eff}, s}$ from 4–9 MHz for each PER. Once $\alpha_{\text{eff}, s}$ was estimated for each PER, the BSC for that PER was estimated as a function of frequency using the reference phantom technique, by inserting the effective attenuation coefficient into Eq. 1. For each subject, the ABSC was computed by averaging the BSC over the 4–9 MHz frequency range used for effective attenuation coefficient estimates. Analogous to previous researchers' use of the integrated backscatter coefficient, our ABSC provides an objective estimate of "echogenicity" (Insana and Hall, 1990). The Effective Scatterer Diameter (ESD) was estimated by obtaining the acoustic form factor from the estimated BSC vs. frequency and fitting a Gaussian form factor model (based on animal studies) by means of square error minimization (Insana and Hall, 1990; Insana et al., 1990). A heterogeneity index of the ESD (ESDHI) was computed using the standard deviation of the ESD within the ROI, ignoring any spatial correlations among estimates. This latter parameter represents the spatial variability among the ESD estimates.

Although we constrained our QUS analysis to homogeneous ROIs, some amount of signal coherence, not readily detected by human interpreters, may have been present due to, for example, periodic structures, a low scatterer number density, or strong isolated reflectors. This can affect the precision of QUS parameter estimations and limit the reproducibility of the results (Rubert and Varghese, 2014; Omaria et al., 2013; Luchies and Oelze, 2015; Rosado-Mendez et al., 2016).

Previous work in our group applied a method for identifying and classifying incoherent and coherent features of the scattering sources in tissue based on an analysis of the RF echo signals. To identify coherence due to a non-stationary process, the generalized spectrum was utilized. The Fourier transform of the RF signal and its conjugate were computed (Rosado-Mendez et al., 2016). Then, the correlation between pairs of frequency components within the bandwidth was quantified, forming one component of the generalized spectrum. In the case of a stationary process, there is no correlation among different frequency components, represented by points off the diagonal of the generalized spectrum. However, when the signals are non-stationary, different frequency components become correlated, and the off-diagonal values of the generalized spectrum are significantly different from zero. A nonparametric approach (collapsed average of the generalized spectrum) was used (Donohue et al., 2001, 2003) to test for coherence. In the collapsed average, the peak at 0 MHz

corresponds to the main diagonal of the generalized spectrum. The presence of peaks in the collapsed average at frequencies other than 0 MHz indicates the presence of non-stationary coherence. The maximum in the collapsed average of the generalized spectrum (maxCA) within a search region (defined by the available bandwidth) is then determined as an indicator of non-stationary coherent scattering (Huang et al., 2000). This parameter was also tested in the classifier.

To quantify coherence due to a stationary process, various parameters from the echo signal envelope were computed over the entire region of interest for each tumor following a raster-scanned, $4 \times 4 \text{ mm}^2$ PER strategy similar to the one used for ESD and ATT. Values within each lesion's ROI were then averaged as a summary metric of echo-signal coherence within the lesion. The signal-to-noise ratio (SNR) of the echo signal envelope was utilized as a model free parameter (Wagner et al., 1983). Based on the SNR, stationary echo signals can be divided into three cases. Diffuse scattering is described with Rayleigh statistics, with $\text{SNR} = 1.91$. Low scatterer number density conditions are described as "pre-Rayleigh" with a $\text{SNR} < 1.9$, and periodically-spaced scattering sources with subresolution spacing are described as "post-Rayleigh" with a $\text{SNR} > 1.9$ (Wagner et al., 1983). Also, the Nakagami model of the statistics of the echo signal amplitude was utilized as a model-based parameter to analyze stationary features (Shankar et al., 2001). The Nakagami distribution probability density function has a closed-form expression, thus making it mathematically tractable, and its parameter estimation is straightforward (Shankar et al., 2001). This simplicity of the Nakagami probability density function makes it possible to define the maximum likelihood estimator (MLE) for the "shape parameter", m , whose value is mainly defined by scattering statistics: $m = 1$ for Rayleigh statistics, $m < 1$ for pre-Rayleigh statistics, and $m > 1$ for post-Rayleigh (Destremes and Cloutier, 2013).

The Shapiro-Wilk test was used to determine whether estimates of each parameter were normally distributed. This was done separately for fibroadenomas and carcinomas. In case of normality, the statistical significance of pair-wise differences in the means of each parameter between fibroadenomas and carcinomas was assessed using a two-sample t-student test. Otherwise, statistical significance was assessed with the Wilcoxon rank-sum test.

Multi-parameter Classifier

Previous studies (D'Astous and Foster, 1986; Mortensen et al., 1996; Nam et al., 2013) suggest that no single acoustic parameter successfully differentiates benign from malignant breast masses. Thus, the approach followed in this study is to test the classification performance of combinations of QUS parameters.

The estimated specific attenuation (ATT), log-average backscatter coefficient ($\log(\text{ABSC})$), effective scatterer diameter (ESD), heterogeneity index of the ESD (ESDHI), maximum collapsed average (maxCA), signal to noise ratio (SNR), and Nakagami shape parameter (Nakagami m) values for each breast mass were used to build two-parameter and three-parameter classifiers. To simplify the task we grouped lesions in two classes: fibroadenomas (benign lesions) and carcinomas (including all types of malignant breast masses due to the limited number). Empirical analysis, based on consultation with statisticians, suggests that a robust test of a multi-parameter classifier to select among two categories (benign and

carcinoma) requires about 10 subjects in each category per parameter. For example, at least 20 subjects per category (at least 40 subjects in total) would be needed to estimate the performance of a two-parameter classifier.

A multivariate classification uses a d -dimensional feature vector (2 or 3 QUS parameters) defining the classifier. The classification is done by comparing the Mahalanobis distance from a feature sample $\vec{x}$ to the feature means $\vec{m}_i$ ($i = 0$ for fibroadenomas, $i = 1$ for carcinomas) of the two classes of a training set. The Mahalanobis distance (Mahalanobis, 1936) is defined as:

$$d_i = \sqrt{(\vec{x} - \vec{m}_i)^T \vec{C}_i^{-1} (\vec{x} - \vec{m}_i)} \quad (4)$$

where $\vec{C}_i$ is the feature covariance matrix of each class. The results of the classification ($\vec{x}$) are assignments to the class with the minimum distance to the centroid of the trained class (Insana et al., 1986; Mather and Tso, 2009; Papoulis and Pillai, 1984).

A “leave-one-out” strategy was used to cross-validate the classification (the entire data set was used for training except one tumor that was left out for testing). An empirical receiver operator (ROC) curve was created by weighting the distance to the centroids to the carcinoma and fibroadenoma classes by a sensitivity factor (ranging between 0.01–1) and by its complement, respectively. The area under the ROC curve (AUC) was used as an overall metric of classification performance. A bootstrapping strategy (100 bootstraps) was used to obtain the mean and 95% confidence intervals of the ROC curve and AUC.

Results

Figure 2 shows plots of individual parameter estimates for each of the 43 tumors. Subjects are presented in these plots ordered from the smallest to largest ROI size to illustrate any potential trend in parameter estimates with ROI size (none was found). Results of the Shapiro-Wilk test demonstrated that estimates of each parameter, except ABSC, were normally distributed. The ABSC was log-normally distributed. Parameter values for breast fat (Nasief et al., 2015) (data point on the far right of each plot) are included in the plots for comparison. All subjects in this study were categorized as US-BIRADS 4 except subjects 23, 24, 33, and 40 which were categorized as US-BIRADS 3, 5, 1, and 5, respectively. Parameter estimates obtained from each subject are also shown in Tables 1 (fibroadenomas) and 2 (carcinomas), ordered from the smallest to largest ROI size. Figures 3 and 4 show scatter plots of the best-performing two-feature combinations (ESD vs. ESDHI and ATT vs. ESD) for fibroadenomas and carcinomas.

The mean ATT estimate among pathology-confirmed fibroadenomas ($1.05 \pm 0.42 \text{ dB} \cdot \text{cm}^{-1} \text{MHz}^{-1}$; mean $\pm$ standard deviation) was lower than the mean ATT among carcinomas ($1.38 \pm 0.64 \text{ dB} \cdot \text{cm}^{-1} \text{MHz}^{-1}$; $p = 0.04$), but both were higher than the mean value for breast fat ($0.73 \pm 0.23 \text{ dB} \cdot \text{cm}^{-1} \text{MHz}^{-1}$). The attenuation coefficient for breast fat reported by D’Astous and Foster (1986) ($4.32 \pm 0.82 \text{ dB} \cdot \text{cm}^{-1}$; measured in a 3–7 MHz bandwidth and estimated by evaluating their power law fit at 7 MHz) was 15% lower than the mean values we previously

reported for breast fat (Nasief et al., 2015) (measured in the bandwidth from 6–12 MHz and also evaluated at 7 MHz).

The mean ABSC estimate among fibroadenomas ($1.5 \pm 1.5 \times 10^{-2} \text{ cm}^{-1} \text{ sr}^{-1}$) was lower than the mean ABSC estimate among carcinomas ($2.9 \pm 3.5 \times 10^{-2} \text{ cm}^{-1} \text{ sr}^{-1}$), although the difference was not statistically significant ($p=0.43$). These values were higher than the mean value for breast fat ($0.7 \pm 0.2 \times 10^{-2} \text{ cm}^{-1} \text{ sr}^{-1}$). Values of the backscatter coefficient of breast fat reported by D'Astous and Foster (1986) and by Nasief et al. (2015) (obtained by evaluating power-law fits reported by both groups at 7MHz) were within a factor of two of each other ($0.0037 \text{ cm}^{-1} \text{ sr}^{-1}$ and $0.007 \text{ cm}^{-1} \text{ sr}^{-1}$, respectively). The backscatter coefficient for IDC reported by D'Astous and Foster (1986) ($1.25 \pm 0.9 \times 10^{-3} \text{ cm}^{-1} \text{ sr}^{-1}$) was more than a factor of 10 lower than the average value among carcinomas found in this study (note the large standard deviations in all cases). This difference could be attributed in part to perfusion in *in vivo* tissue, as well as to differences in the collagen-rich extracellular matrix between *in vivo* and *ex vivo* samples.

The mean ESD among fibroadenomas ($108 \pm 24.1 \text{ } \mu\text{m}$) was higher than the mean ESD among carcinomas ($78.3 \pm 15.7 \text{ } \mu\text{m}$, $p=7.6\text{e-}05$), and both are larger than the mean value found in breast fat ($60.0 \pm 9.3 \text{ } \mu\text{m}$). The mean ESDHI estimate among fibroadenomas ($13.1 \pm 2.4 \text{ } \mu\text{m}$) was higher than the value among carcinomas ($10.1 \pm 4.4 \text{ } \mu\text{m}$, $p=0.006$), and both were larger than the mean value found in breast fat ($3.7 \pm 1.7 \text{ } \mu\text{m}$).

The mean maxCA estimate among fibroadenomas (0.09 ± 0.06) was comparable to the value in carcinomas (0.12 ± 0.07 , $p=0.26$), and both are not significantly different from the mean value found in breast fat (0.05 ± 0.04). The mean SNR estimate among fibroadenomas (1.17 ± 0.37) was comparable to the value in carcinomas (1.2 ± 0.34 , $p=0.73$), and is close to the mean value found for breast fat (1.49 ± 0.21). The mean Nakagami m estimate among fibroadenomas (0.56 ± 0.19) was not different from the values in carcinomas (0.58 ± 0.19 , $p=0.75$), and both were close to the mean value found in breast fat (0.72 ± 0.18).

When parameters were combined and applied to the Mahalanobis distance classifier, it was possible to distinguish the masses proven to be fibroadenomas from those that were cancers. Examples of ROC curves illustrating this are shown in Fig. 5. Table 3 lists AUC values and the corresponding 95% confidence intervals for various two- and three-parameter combinations used in the classifier. The best two-parameter classification performance (largest AUC value) was obtained with ESD and ESDHI (AUC=0.979, 95% CI [0.946,1.000] Fig. 5(a)), and the best three-parameter classification performance was obtained with ATT, ESD, and ESDHI (AUC=0.999, 95% CI [0.995,1.000], Fig. 5(b)) followed by the use of log(ABSC), ESD, and ESDHI (AUC=0.986, 95% CI [0.963,1.000] in Fig. 5(c)). The supplementary file MAHALANOBIS_PercentileBootstrap.m is a MATLAB script that creates the Mahalanobis distance classifier with ESD, ESDHI, and ATT, creates the ROC curve, and estimates the AUC and confidence intervals. The separation among fibroadenomas and carcinomas with ATT, ESD, and ESDHI can be observed in Fig. 6, which shows each fibroadenoma and each carcinoma in a 3D space defined by these parameters. The use of Nakagami m and echo-amplitude SNR consistently degraded the classification performance.

Discussion

A simple, data-driven, multi-parameter Mahalanobis classifier based on system-independent estimates of acoustic properties of tissue appears to be an effective approach to increase the specificity of breast ultrasound and to identify those lesions that are least likely to be carcinomas. This possibly results from the ability to compensate for system-dependent effects such as the system transfer function and diffraction through the use of the Reference Phantom Method. This is in part supported by the hindering effect on classification performance of parameters based on speckle statistics, i.e., the Nakagami m and the echo amplitude SNR. These parameters depend on the size of the pulse volume, which is directly affected by the diffraction field (Rosado-Mendez et al., 2014). The improvement in breast lesion classification over previous studies reported in the Introduction might be due to the optimization of different stages in the signal processing strategy, such as the use of a multitaper estimator of the echo signal power spectrum (Rosado-Mendez et al., 2013) and the use of the modified least-squares attenuation compensation method (Nasief et al., 2015).

As described in the Introduction, various statistical and machine learning-based classifiers have been proposed to characterize breast tissue. Although the goal of the work reported here was not to select the best classification strategy, some of these methods were also tested using leave-one-out cross-validation and bootstrapping with 100 boots to obtain the 95% confidence intervals of the AUC. MATLAB implementations of the naïve Bayesian, Support Vector Machine (SVM) and k-Nearest Neighbor (kNN) classifiers to ESD, ESDHI and ATT yielded AUC=0.956, 95% CI [0.868, 0.995], AUC=0.993 [0.960, 1.000], and AUC=0.869 [0.732, 0.951], respectively. Using the best performing 2-parameter combination (ESD and ESDHI), we found AUC=0.944 [0.855, 1.000] for a naïve Bayesian classifier, AUC=0.963 [0.938, 0.983] for SVM, and AUC=0.819 [0.718, 0.915] for the kNN. The advantage of the Mahalanobis-distance classifier is that it is model-free (does not require any assumption regarding the statistical distribution of the data) and is fully data-driven. Having a data-driven classifier, rather than a model-based one, facilitates the reproducibility and translation of this classification strategy by removing the need to demonstrate compliance to statistical assumptions and being easy to implement.

An interesting finding was that the backscatter coefficient estimates for tumors were higher than previously reported values for breast fat (Nasief et al., 2015). This seemed counter-intuitive because most lesions appeared hypoechoic on B-mode images when compared to surrounding fat. Although we do not fully understand this result, it could possibly be attributed to the presence of sources of coherent scattering within lesions. This is addressed in Fig. 7, which shows a scatter plot of the logarithm of ABSC and maxCA for fibroadenomas, carcinomas, and breast fat. The positive correlation ($R^2=0.49$, 95% CI [0.2,0.7]) among these two variables supports this conjecture. Another possible contributor to the hypoechoic appearance of tumors with respect to breast fat on B-mode images is their higher attenuation compared to that of surrounding breast fat (about $1.4 \text{ dB}\cdot\text{cm}^{-1}\text{MHz}^{-1}$ vs $0.7 \text{ dB}\cdot\text{cm}^{-1}\text{MHz}^{-1}$). Higher attenuation within a mass usually leads to posterior acoustic shadowing of distal structures. It would also cause decreased echo amplitudes for scatterers within the mass itself, particularly those near its distal margins, and thus, it may be a contributor to the hypoechoic appearance of a highly-attenuating mass on ultrasound images.

As we expand these studies, we hope to corroborate and further clarify the nature of this observation.

Separation between fibroadenomas and cancers is larger for single parameters in this study compared to that reported by Nam et al. (2013). Several advances in signal processing and parameter estimation were used in this study that were not implemented at the time of the manuscript by Nam, et al. For example, a multi-taper method for power spectral estimation, a modified least squares method for intervening-tissue attenuation compensation (that does not assume a linear frequency dependence of attenuation), and echo signal coherence analysis (each described in the Methods section) were used in this work. Each of these provided improved parameter estimates (lower estimate bias and variance) compared to results reported by Nam, et al.

This study has various limitations. The limited number of cases available enabled the QUS classifiers identified in Table 3 to be only marginally trained and tested. Thus, we only tested the combination of 2 or 3 QUS parameters to avoid overfitting, and we did not attempt to introduce additional quantitative feature combinations into the process. Future studies might include more features combinations in the classifier. However, based on consultation with statisticians, to robustly test a 5-parameter classifier to select among two categories (benign and carcinoma), and assuming that 10 subjects are needed in each category per parameter, at least 50 subjects per category (at least 100 subjects in total) would be needed.

Also related to the small number of subjects in this study is the inclusion of data from two studies. RF echo signals from both groups were obtained using comparable transducers and reference phantoms. We have recently shown that the echo signal power spectra of a system used in this study are highly replicable (Guerrero et al., 2018). Even though the patients in the first subgroup were scanned under a custom elasticity imaging mode with a different model system, QUS parameters were estimated from the initial RF echo signal frame (before compression), which was analogous to the protocol of the second subgroup. In addition, data from both groups were collected by the same researchers. Based on these arguments, data were combined to improve the statistical power of the classification.

Finally, classifier performance reported here is biased (optimistically) because the data entering into the study were preselected to be either fibroadenomas (the only benign disease included) or carcinomas (all cancer types combined into a single class). That reduction in task complexity greatly simplifies the performance requirements compared to the clinical task of breast mass characterization. Further, tumors selected for inclusion had reasonably large regions that were (subjectively) homogeneous. This likely reduced variability in parameter estimates and improved classifier performance. Classification into these categories (“carcinoma” and “fibroadenoma”) is insufficient for clinical practice. A more useful classification would include all cancer types, all benign breast masses, and various types of normal tissue. We are currently extending our study towards this aim.

Conclusions

A model-free, multi-parameter Mahalanobis distance classifier based on system-independent QUS parameters has the potential to differentiate fibroadenomas from cancerous masses in the breast. Performance of the classifier incorporating two features (ESD and ESDHI) resulted in an area under the ROC curve of 0.98, while a three feature set (ESD, ESDHI and ATT) yielded an area under the ROC curve of 0.999. Results from the three-parameter classifier have to be interpreted with caution due to the limited number of subjects in this study. A larger study is needed to increase the diversity of benign diseases included and to perform a more rigorous test of the classifier performance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

A region of interest (ROI) for parameter estimation was chosen within a B-mode image. That ROI was further partitioned into power spectral density estimation regions (PSER), and, depending on the parameter being estimated, data from one or more of those PSERs was used in a parameter estimation region (PER). For example, backscatter coefficient estimation was performed on each PSER, but estimating attenuation required estimating the power loss as a function of depth among a sequence of PSERs in a single PER. The dots signify the center of each PSER.

Figure 2:

Plots of the individual QUS parameter estimates for each subject ordered from smallest to largest ROI size. The same ROI was used for all parameter estimates for an individual subject (e.g., FA1 is the fibroadenoma with the smallest ROI). ROI sizes are shown in Tables 1 and 2. Fibroadenoma (FA) are shown separately from cancers. Cancers are grouped together by type: Invasive ductal carcinoma (IDC); Invasive lobular carcinoma (ILC). The solid horizontal lines show the median value of that parameter (separately for fibroadenoma and carcinoma), and the dashed lines show the interquartile range of values

Figure 3:
Plot of ESDHI vs ESD for fibroadenomas and carcinomas

Figure 4:
Plot of ATT vs ESD for fibroadenomas and carcinomas

Figure 5:

Receiver operating characteristic curves illustrating the performance of various classifiers based on combinations of quantitative ultrasound parameters. (a) Effective scatterer diameter (ESD) and its heterogeneity index (ESDHI). (b) Specific attenuation (ATT), ESD and ESDHI. (c) Log-transformed average backscatter coefficient (ABSC), ESD and ESDHI.

Figure 6:
Plots of best 3 parameters combination

Figure 7:
Average backscatter coefficient versus maxCA for fibroadenomas, carcinomas and fat.

Table 1:

QUS parameter values of fibroadenomas included in this study presented in the order from smallest to largest ROI size (the same order as in fig. 2). The sequential order in which they were recruited into the study is shown in the “subject” column. Parameters include specific attenuation (ATT), effective scatterer diameter (ESD), heterogeneity index of the ESD (ESDHI), average backscatter coefficient (ABSC), signal to noise ratio (SNR), Nakagami shape parameter m , and maximum collapsed average (maxCA). Subjects 28 and 30 were fibroadenoma with sclerosing adenosis and fibrocystic change. Subject 37 was reported as benign breast tissue with architecture suggestive of fibroadenoma. Units: ATT: $\text{dB}\cdot\text{cm}^{-1}\text{MHz}^{-1}$, ESD: μm , ESDHI: μm , ABSC: $\text{cm}^{-1}\text{sr}^{-1}$, Size: mm^2

Class	ATT	ESD	ESDHI	ABSC	SNR	Nakagami	maxCA	ROI size	subject
FA1	0.74	81.8	14.2	0.0213	1.63	0.83	0.109	5×5	22
FA2	1.25	94.2	13.6	0.0460	0.71	0.29	0.144	5×5	35
FA3	1.55	109.4	12.8	0.0360	1.15	0.53	0.057	5×5	37
FA4	1.57	124.8	10.8	0.0019	1.31	0.64	0.052	6×6	9
FA5	0.68	59.5	16.7	0.0025	0.85	0.35	0.076	6×6	27
FA6	0.69	107.2	11.4	0.0076	1.49	0.72	0.080	6×6	28
FA7	1.94	147.1	12.1	0.0480	1.28	0.59	0.093	5×8	41
FA8	0.71	143.6	10.4	0.0003	1.17	0.56	0.139	7×6	13
FA9	1.00	87.0	15.1	0.0094	1.13	0.55	0.008	7×6	15
FA10	0.85	112.3	13.6	0.0090	0.45	0.21	0.101	8×6	21
FA11	0.76	87.5	12.9	0.0030	1.21	0.57	0.161	8×6	30
FA12	1.24	119.0	11.8	0.0390	0.83	0.39	0.060	7×7	31
FA13	1.19	116.7	15.3	0.0460	0.80	0.38	0.239	6×9	43
FA14	1.92	165.5	11.8	0.0013	0.63	0.50	0.121	8×7	12
FA15	0.67	96.1	17.5	0.0170	1.19	0.59	0.033	9×7	3
FA16	1.30	90.1	15.6	0.0100	1.47	0.76	0.040	9×7	14
FA17	1.04	93.2	13.1	0.0212	1.13	0.54	0.177	8×10	32
FA18	1.05	127.5	10.6	0.0020	0.97	0.46	0.033	14×7	8
FA19	1.20	145.0	10.6	0.0064	1.80	0.88	0.006	10×10	1
FA20	0.42	82.9	20.0	0.0143	1.48	0.72	0.094	12×9	16
FA21	0.76	112.5	10.7	0.0013	0.89	0.42	0.112	15×9	2
FA22	1.01	104.8	9.8	0.0003	1.57	0.79	0.152	16×9	29
FA23	1.69	131.2	12.9	0.0090	1.02	0.47	0.029	15×10	7
FA24	1.14	100.5	10.9	0.0030	1.32	0.62	0.161	15×12	5
FA25	0.36	95.3	14.5	0.0221	0.64	0.27	0.114	16×12	23
FA26	0.71	85.6	13.4	0.0120	1.52	0.73	0.169	15×15	6
FA27	0.89	96.8	12.5	0.0092	1.89	1.01	0.013	15×15	20

Table 2:

QUS parameter values of malignant masses included in this study presented in the order from smallest to largest ROI size (the same order as in fig. 2). The sequential order in which they were recruited into the study are shown in the “subject” column. Parameters include specific attenuation (ATT), effective scatterer diameter (ESD), heterogeneity index of the ESD (ESDHI), average backscatter coefficient (ABSC), signal to noise ratio (SNR), Nakagami shape parameter m , and the maximum collapsed average (maxCA). ACA = adenocarcinoma; IDC = invasive/infiltrating ductal carcinoma; DCIS = ductal carcinoma *in situ*; ILC = invasive/infiltrating lobular carcinoma; LCIS = lobular carcinoma *in situ*; IPC = intracystic papillary carcinoma. Subject 38 was reported as DCIS involving intraductal papilloma and involving ducts adjacent to papilloma; Subject 42 was reported as infiltrating ductal carcinoma Nottingham Grade 2, LCIS classical type, metastatic breast ductal carcinoma. Units: ATT: $\text{dB}\cdot\text{cm}^{-1}\text{MHz}^{-1}$, ESD: μm , ESDHI: μm , ABSC: $\text{cm}^{-1}\text{sr}^{-1}$, ROI Size: mm^2

Class	ATT	ESD	ESDHI	ABSC	SNR	Nakagami	maxCA	ROI size	subject
IDC1	1.85	90.1	10.1	0.005	1.45	0.73	0.204	5×5	18
IDC2	2.19	68.3	8.5	0.039	1.28	0.59	0.195	5×5	39
IDC3	2.17	57.9	13.1	0.041	1.24	0.56	0.206	5×5	40
IDC4	0.85	54.0	14.0	0.115	1.36	0.64	0.213	6×5	36
IDC5	1.47	109.3	6.2	0.075	1.19	0.53	0.149	5×7	34
IDC6	1.48	68.6	12.3	0.007	0.69	0.37	0.061	8×6	11
IDC7	0.63	95.9	2.4	0.006	1.17	0.54	0.034	7×6	25
IDC8	1.09	81.9	11.1	0.002	1.62	0.86	0.105	8×8	42
IDC9	2.2	86.7	6.2	0.001	1.29	0.59	0.004	13×10	17
IDC10	1.03	80.2	11.3	0.002	2.06	1.16	0.009	12×12	19
ILC1	0.74	94.7	5.1	0.016	1.13	0.51	0.123	5×5	26
ILC2	0.52	87.2	6.2	0.015	1.20	0.57	0.084	8×6	24
IPC	0.50	58.5	7.5	0.028	0.91	0.40	0.084	14×12	33
ACA	1.30	77.4	13.6	0.094	0.91	0.50	0.172	6×5	10
DCIS1	1.92	79.1	15.6	0.001	0.68	0.34	0.140	5×5	38
DCIS2	2.20	62.8	18.9	0.016	1.13	0.53	0.107	7×6	4

Table 3:

Area under the receiver operating characteristic curves for various 2-parameter and 3-parameter combinations of QUS parameters forming a multi-parameter classifier to differentiate fibroadenomas from carcinomas. The 95% confidence intervals were computed separately for the case when fibroadenoma was true-positive

2 Parameters	AUC	95% Confidence interval
ESD, ESDHI	0.979	[0.946,1.000]
ESD, ATT	0.872	[0.738,0.963]
ESD, log(ABSC)	0.792	[0.581,0.938]
ESD, SNR	0.758	[0.600,0.903]
ESD, Nakagm	0.753	[0.569,0.895]
3 Parameters		
ESD, ESDHI, ATT	0.999	[0.995,1.000]
ESD, ESDHI, log(ABSC)	0.986	[0.963,1.000]
ESD, ESDHI, SNR	0.971	[0.936,1.000]
ESD, ESDHI, Nakagm	0.962	[0.923,0.999]