Quantitative ultrasound assessment of breast cancer using a multiparameter approach

Michael L. Oelze and William D. O'Brien, Jr.
Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois, Urbana, IL 61801 USA

James F. Zachary
Department of Pathobiology, University of Illinois, Urbana, IL 61802 USA

***Abstract*—Early detection and diagnosis of breast cancer leads to improved prognosis. Quantitative ultrasound (QUS) techniques utilizing a multiparameter set have been developed for classifying rodent models of breast cancer. The improvement in detection and diagnosis of breast cancer using QUS will have significant medical impact. Two kinds of mammary tumors, carcinoma and sarcoma, were examined in mice using QUS imaging. Ten tumors for each kind of cancer were scanned with a 20-MHz single-element transducer (f/3). The tumors contained microstructural differences in size, shape, and organizational patterns of the scatterers. Cells were identified as a prominent source of scattering in the tumors. The average scatterer diameter (ASD) and average acoustic concentration (AAC) were estimated by comparing the normalized backscattered power spectra from the tumors with newly developed models of cell scattering. The organizational structure of the tumors was also characterized by a clustering parameter (the β parameter) and the randomness of the scatterer locations (the S parameter) by comparing the envelope statistics of the backscatter to a homodyned-K distribution. F-tests conducted on the backscattered power spectra from the two kinds of tumors revealed statistically significant differences for frequencies above 16 MHz. QUS images of the tumors utilizing the ASD, AAC, β, and S parameter estimates from the new model and the envelope statistics were constructed. Statistically significant differences were observed between the carcinomas and sarcomas for all estimated parameters for ultrasonic frequencies above 16 MHz. Feature analysis plots incorporating all four parameters indicated cancer classification was improved compared with analysis using only two parameters. High-frequency QUS utilizing a multiparameter feature set improved the diagnostic potential of ultrasound for breast cancer detection. (Supported by NIH Grants CA 079179 and CA111289)**

Keywords-backscatter; tissue characterization; quantitative ultrasound; envelope statstics

I. INTRODUCTION

The American Cancer Society (ACS) indicates that breast cancer is the most common cancer among women and is the second leading cause of cancer death in women [1]. It is estimated that 212,920 women in the USA will be found to have invasive breast cancer in 2006 [1]. In addition to invasive breast cancer, 61,980 cases of in situ breast cancer are expected with approximately 85% diagnosed as ductal carcinoma in situ (DCIS) [1]. About 41,430 women will die from the disease. However, death rates due to breast cancer have decreased by 2.3% per year from 1990 to 2002 because of earlier detection, improved treatment, and increased awareness [1]. As suggested by the ACS, breast self examination, clinical breast examination (palpation) and mammography are the three most frequently used diagnostic tools for detecting breast abnormalities. The prognosis for breast cancer patients is best when the disease is detected at an early stage.

Improving the specificity of breast diagnosis through an imaging modality such as ultrasound, will improve overall diagnostic accuracy. One way to improve the specificity of diagnosis is through quantitative ultrasound (QUS) from the backscatter. QUS techniques parameterize the ultrasound signals backscattered from tissues and relate these parameters to tissue microstructure. The quantifiable parameters relate microstructural information to specific tissue locations (imaging) thereby improving the diagnostic potential over conventional ultrasonic imaging.

II. RESULTS OF PREVIOUS STUDIES

Several studies have been conducted over a broad ultrasonic frequency range (5 to 25 MHz) to examine the capabilities of quantitative ultrasound to detect and diagnose disease, particularly solid mammary tumors in rats and mice [2-5]. In the first study, spontaneous mammary fibroadenomas were examined using QUS over a frequency range of 5 to 12 MHz and compared with normal rat mammary tissue [2]. Scatterers were modeled using a spherical Gaussian form factor (FF) [6].

The findings of the first study indicated that QUS was able to differentiate between the fibroadenomas and surrounding healthy tissue because statistically significant differences were observed in the average scatterer diameter (ASD) and average acoustic concentration (AAC) parameters. The acoustic concentration is defined as the product of the scatterer number density times the square of the impedance difference between the scatterer and background [7]. The estimates of ASD in the fibroadenomas were compared with optical photomicrographs of the tumors. Qualitative relationships were observed between the ASD estimates and the acini in the fibroadenomas, i.e. the sizes of the estimates matched the average sizes of the acini.

The success of QUS to differentiate between fibroadenomas and normal tissue in rats and the new innovations in QUS processing led to a more complete study that compared the benign fibroadenomas with a malignant form of breast cancer in mice [3]. The second tumor examined was from a commercially available tumor cell line, the 4T1 MMT carcinoma for mice (ATCC, Manassas, VA). The carcinoma cells were cultured in medium and then injected subcutaneously into the fatpad of balb/c mice. Tumors were grown to a little over a centimeter in size and then examined using QUS techniques. The 4T1 mouse mammary tumor was chosen because of its homogeneous cytologic characteristics and because the tumors are models for stage IV human breast cancer in growth patterns [8,9]. Initially, the same transducer used to scan the rats was used to scan the mice. Subsequent ASD estimates suggested the *ka* value (the acoustic wave number times radius of the scatterer) was small (< 0.5). Therefore, a new single-element focused transducer (f/3) with center frequency of 20 MHz was used. The analysis bandwidth with the new transducer was 10 – 24 MHz.

The next study [4,5] examined three animal models for breast cancer: the mammary fibroadenomas, the mammary carcinomas and a mammary sarcoma (EHS sarcoma (ATCC, Manassas, VA) for mice) [10]. Sarcoma cells were injected into mice (C57BL/6) and tumors were allowed to grow to a little over a centimeter in size before scanning. Initially, the 10-MHz center frequency transducer was used to scan the tumors and it was also found that the *ka* value was small (< 0.5). The 20-MHz center frequency transducer was subsequently used to obtain QUS estimates.

A distinct difference was observed between fibroadenomas with larger ASDs and the carcinomas and sarcomas with the smaller ASDs. However, the QUS analysis using the spherical Gaussian FF over the analysis bandwidth of 10 to 24 MHz was insufficient to separate the carcinoma from the sarcoma. Using the conventional spherical Gaussian FF, the carcinomas and sarcomas appeared almost identical.

F-tests of the normalized backscattered power spectra from the two kinds of tumors revealed statistically significant differences existed when the frequency of ultrasound was above 16 MHz [5]. Therefore, differences that existed in the RF backscattered signature were not detected using the spherical Gaussian FF over the initial analysis bandwidth of 10 to 24 MHz. The inability of QUS over the initial frequency analysis bandwidth to detect the microstructural differences observed from optical photomicrographs of the carcinomas and sarcomas suggested two possibilities: 1) An appropriate analysis bandwidth needed to be used and/or 2) more appropriate models that could detect the different features needed to be developed.

A new model for scattering was proposed [4]. The new model was based on the finding that cells were a dominant source of scattering in the carcinomas and sarcomas [5]. A new cell model (NCM) was developed and used to model scattering from the cell composed of both a nucleus and cytoskeleton. ASD estimates using the NCM were hypothesized to represent the average nuclear diameter. In addition, the analysis bandwidth used was 16 to 27 MHz based on the findings from F-tests that revealed statistically significant differences in the power spectra of the carcinomas and sarcomas above 16 MHz.

The NCM was developed from a closer examination of the cellular structure. Any model of scattering from the cell should take into account the cytoskeletal structure as well as the nuclear structure. The cytoskeletal structure is made up of the actin filaments, microtubule networks and other cellular organelles. The cytoskeletal structures are important components in determining the density and compressibility of the cell body (outside the nucleus).

The NCM was constructed based on the idea that the density and compressibility of the cytoskeletal structure played an important role in cellular scattering in tissues. Figure 1 shows a diagram of the cellular structures proposed as key to modeling the cell acoustically. The network of actin filaments that criss-cross throughout the cellular cytoplasm determines the underlying density and compressibility of the cell [11-13]. According to literature values, the nucleus has different mechanical (i. e. acoustic) properties from the actin filaments and microtubules. The microtubules attach to the nucleus and fan out radially from the nucleus to the edges of the cell. It is conjectured that the microtubules increase the overall density and reduce the compressibility of the cytoplasm (acoustic impedance values). Because the microtubule networks are bundled more densely at the surface of the nucleus and less densely at the cell edges, the impedance of the cell is modeled as a continuously increasing value from the edge of the cell to the nucleus. Figure 2 shows a diagram of the modeled impedance value with increasing cell radius (assuming a spherical cell) including the cytoskeletal structure.

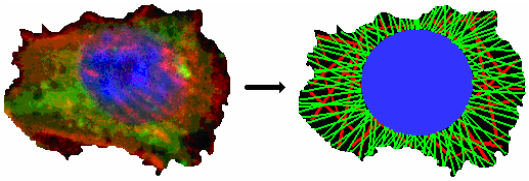


Figure 1. Confocal microscope image of stained carcinoma cell (left) and simplified model (right) with nucleus (blue), actin filaments (red), and microtubules (green).

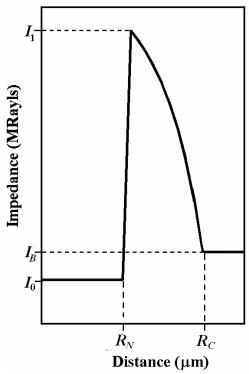


Figure 2. Acoustic model of spherical cell including effects of cytoplasm, cytoskeleton and nucleus. I_1 is the impedance at the edge of the nucleus, I_B is the imepdance of the background, I_0 is the impedance of the nucleus, R_N and R_C are the radii of the nucleus and total cell, respectively.

The NCM was used to construct a 3D spatial autocorrelation function of the cell. From the 3D spatial autocorrelation function, the theoretical backscattered power spectrum (form factor) was calculated. The normalized backscattered power spectrum was converted to a measured FF from the carcinomas and sarcomas and then fit to the theoretical FF model for the NCM. The ASD ($2R_N$) was estimated from fits of the NCM to the measured data. The NCM FF model was fit to the measured FF by using a Monte Carlo technique over five values (I_B, I_I, R_N, R_C, and a gain factor). The analysis bandwidth used was 16 to 27 MHz based on the findings from F-tests that revealed statistically significant differences in the power spectra of the carcinomas and sarcomas above 16 MHz.

Statistically significant differences were observed using only the ASD and AAC estimates between the carcinomas and sarcomas with the new model and over the analysis bandwidth of 16 to 27 MHz. While a statistically significant difference could be observed between estimates from the carcinomas and sarcomas, many of these estimates were overlapping, i.e., some of the carcinomas could be easily misclassified as sarcomas. To improve the ability to separate the tumors based on ultrasonic scattering properties and to expand the feature set used for classification, envelope statistics were examined.

III. Envelope Statistics

Previous research suggested that backscatter from tumors was in some cases highly dependent on the organization of the cells in the tumor [14,15]. Closer examination of the photomicrographs of the carcinomas and sarcomas (Fig. 3), suggested that the organizational patterns were the prominent features distinguishing the microstructure. The carcinomas contained a uniform distribution of cells of nearly the same size. Because the cells were of nearly the same size and were tightly grouped together, the assumption of randomly spaced scatterers may not have been entirely accurate. Similarly, the sarcoma consisted of cells of about the same size but grouped in clusters ranging from a single cell to groups of twenty and surrounded by a fluid-like extracellular matrix.

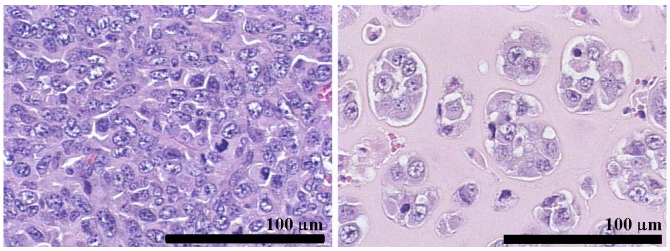


Figure 3. Optical photomicrographs of (left) a carcinoma tumor and (right) a sarcoma tumor.

Organizational differences from the tumors were characterized using envelope statistics. The homodyned K distribution was used to model the amplitude of the envelope from ROIs in the carcinomas and sarcomas [16]. The homodyned K distribution yields two parameters: the S parameter quantifies the randomness of the scatterer spacings and the β parameter, called the clustering parameter, quantifies the amount of clustering of the scatterers in the interrogated tissue. When the S parameter is zero, the scattering medium is considered to be truly random (Rayleigh distribution).

Only the first three moments of the homodyned K distribution were calculated. The resulting probability distribution function (pdf) from the first three moments was then compared to the pdf from the backscattered signals. The minimum mean square difference between the pdf calculated from the measured data and the theoretical pdf was found by varying the S parameter and the β parameters. An example of a pdf estimated from the backscatter envelope along with the best-fit homodyned K pdf and a Raleigh pdf (S parameter equals zero) are shown in Fig. 4.

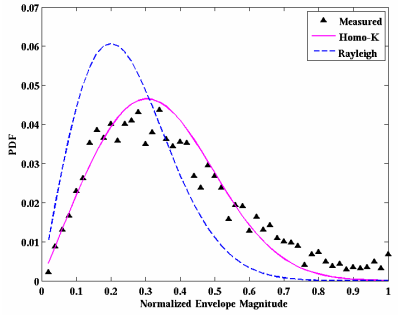


Figure 4. Pdfs estimated from the backscatter measurements versus theoretical pdfs.

Estimates of the S parameter and the β parameter were obtained from backscattered envelope signals corresponding to ROIs in the carcinomas and sarcomas. Because the parameters corresponded to the same ROIs used to estimate the ASD and AAC, parameter images could be formed using the S and β parameters (Fig. 5).

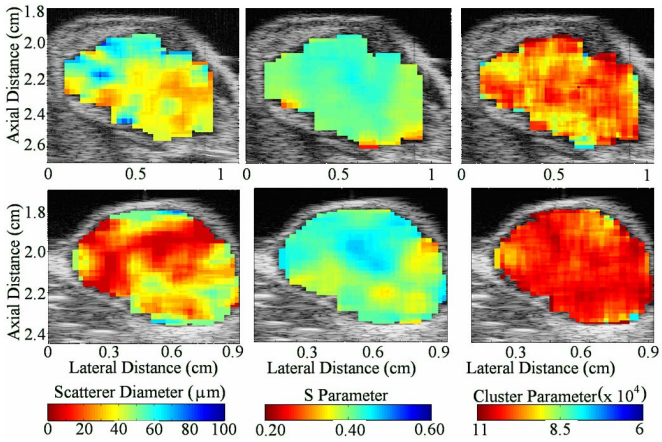


Figure 5. Parameter images of carcinoma tumors (top panels) and sarcomas (bottom panels).

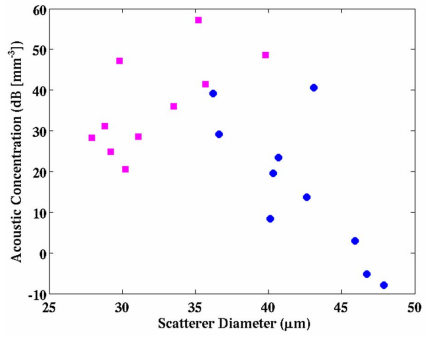
IV. Results and Discussion

Table II lists the estimates of the S and β parameters along with the ASD and AAC parameters using the NCM. For each parameter, a statistically significant difference was observed between the carcinomas and sarcomas using ANOVA.

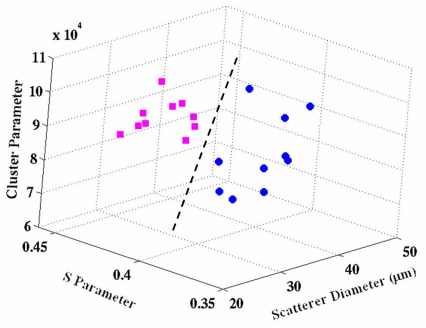
TABLE I. MEAN ESTIMATES OF ASD, AAC, β, AND S PARAMETERS FROM TEN CARCINOMAS AND TEN SARCOMAS WITH STANDARD DEVIATIONS

	ASD (μm)	*AAC (dB)*	*β*	*S*
Carcinoma	41.2 ± 1.39	16.4 ± 17.1	7.9 ± 1.1	0.41 ± 0.016
Sarcoma	34.4 ± 5.95	36.4 ± 11.9	9.1 ± 0.78	0.43 ± 0.015
	P < 0.05	P < 0.05	P < 0.05	P < 0.05

Using a multiparameter approach to classify tissues increases the ability to separate tissues that may be closely related in structure. The improvement in classification due to a multiparameter approach can be observed by comparing the feature analysis plots of Fig. 6a and Fig. 6b. From Fig. 6a, while statistically significant differences were observed using only the ASD and AAC estimates between the carcinomas and sarcomas, the overlap between the estimates was considerable making it difficult to draw a line clearly demarcating the two kinds of tumors. However, when a third parameter was added as in Fig. 6b, the demarcation between the carcinomas and the sarcomas became more apparent as is illustrated by the dashed line separating the sarcomas from the carcinomas. As more parameters are added yielding a higher dimensional set, the ability to separate different tissues increases.



(a)



(b)

Figure 6. Feature analysis plot of (a) ASD versus AAC and (b) ASD versus the S parameter versus the β parameter with the carcinomas, ●; and the sarcomas, ■.

V. CONCLUSION

Quantitative ultrasound has been used to characterize mammary tumors in rodent models of breast cancer. Specifically, a multiparameter approach (consisting of four parameters) to classification was demonstrated to outperform an approach consisting of only two parameters. The first two parameters were the ASD and AAC determined from the backscattered power spectrum from tissues. The second two parameters were the S parameter and the β parameter derived from the envelope statistics of the backscatter. Improved models for scattering and choice of an appropriate analysis bandwidth were also found to be significant for classifying tissues with similar structure.

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