Chapter 2
Quantitative Ultrasound History and Successes

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Abstract Ultrasound has been used for imaging and diagnostics for more than 50 years. During that time, the number of medical applications for ultrasonic imaging has increased dramatically. These increases in applicability have come with improved device technology, improved understanding of ultrasound interaction with tissues, and improved processing techniques. Over the past three decades, quantitative ultrasound (QUS) techniques have been explored to further improve medical diagnostics and monitor/assess therapeutic responses. The acceptance of QUS techniques has been slower in common medical practice than conventional ultrasonic imaging techniques like B-mode or Doppler. This is due mainly to a lack of technological capabilities to make use of these unique and beneficial imaging modes. However, with modern ultrasonic imaging devices, QUS techniques have found a new acceptance and are poised to make significant contributions to diagnostic medicine. In this chapter, we will examine the history of QUS techniques and their evolution over time along with significant contributions and successes that have been demonstrated over the years.

Keywords Quantitative ultrasound · Tissue characterization · Spectral analysis

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2.1 Introduction

The earliest history of the science of sound has been recorded by Hunt (1978) in his manuscript that was completed following his untimely death. Another interesting and readable history of acoustics was prepared by Lindsey (1966). Hunt recounts the period from antiquity to the age of Newton, and Lindsey brings us mostly to the age of Rayleigh with special emphasis on Rayleigh's impact on modern acoustics. Sir Isaac Newton put forth the first serious theory regarding sound being a wave in his 1687 *Principia Mathematica* (Newton 1687). Modern acoustics as we know it today was first formulated in the classic 1877 work *The Theory of Sound* by Lord Rayleigh (Rayleigh 1945).

The development of diagnostic ultrasound applications dates back to the 1930s (Gohr and Wedekind 1940). The Dussik brothers developed a through-transmission differential attenuation method to image the brain (Dussik 1942, 1948, 1949; Dussik et al. 1947), although their technique was never widely developed for clinical application. Shortly thereafter, Firestone's patent (1942) for flaw detection in metals, and his later demonstration, is considered the first modern pulse-echo ultrasound technique for flaw detection (Firestone 1945, 1946; Firestone and Frederick 1946), and the basis for pulse-echo imaging in medicine. The development of diagnostic ultrasound instrumentation as we know it today was initiated around the time of the end of the Second World War; a time when fast electronic circuitry was becoming available as a result of the wartime RADAR and SONAR efforts, both of which utilized the pulse-echo principle. In the late 1940s and early 1950s, it was demonstrated that tissue interfaces could be detected in ultrasound echoes (Howry 1952), that tissue structure could be differentiated (cancer from benign) in ultrasound echoes (Wild 1950; Wild et al. 1950; French et al. 1950; Wild and Neal 1951), and that gall stones could be detected in ultrasound echoes (Ludwig and Struthers 1950), all of these being A-mode applications. Later, Howry and Bliss (1952) and Wild and Reid (1952a, b) independently built and successfully demonstrated the earliest B-mode, bistable, ultrasound scanners.

By the early to mid 1950s, the basic ideas of producing and acquiring reflected ultrasound echoes using either water path or direct contact methods, and displaying them in either A-mode or B-mode formats had been identified. These early investigators made their observations and findings public through presentations and publications which no doubt stimulated others to pursue pulse-echo system improvements and/or diagnostic imaging applications in, for example, echoencephalography (Leksell 1955; Gordon 1958; Tanaka et al. 1960), ophthalmology (Mundt and Hughes 1956; Baum and Greenwood 1958a, b), echocardiography (Elder and Hertz 1954; Elder and Gustafson 1957), obstetrics and gynecology (Donald and Brown 1961; Donald 1974), breast (Hayashi et al. 1962), direct-contact two-dimensional ultrasonic scanner (Donald 1964; Holmes et al. 1965), ultrasonic scanner with two articulated arms (Wells 1966; Filipczynski et al. 1966) and dynamic focusing (Reid and Wild 1957). However, progress was modest and the bistable images were often challenging for diagnostic interpretation in the late

1950s and 1960s. It was a time when most of the progress was being made in the university and/or hospital settings by true pioneers.

The 15-year period between the early 1970s and mid 1980s witnessed the greatest expansion of diagnostic ultrasound imaging capabilities, starting with bistable, static and ending with grey-scale, real-time capabilities. One of the major ultrasonic image quality advances was the introduction of the grey scale (Kossoff and Garrett 1972; Kossoff et al. 1974). Another major advance was the ability to display images in real time, wherein there were a number of approaches including the mechanical scanner (Griffith and Henry 1974), the linear array (Bom 1973; Bom et al. 1973), the phased array (Somer 1968; von Ramm and Thurston 1972; Thurston and von Ramm 1974), and the water-path scanner (Carpenter and Kossoff 1977). Scan converter developments played an important role with the implementation of both grey-scale and real-time capabilities (Fry et al. 1968; Yokio and Ito 1972).

2.2 Attenuation and Propagation Speed

Along with advances in ultrasound scanner technology came a deeper understanding of the wave propagation properties of tissues, which would define image contrast mechanisms and the fundamental limits of penetration depth and frame rate. One of the earliest reports of ultrasonic propagation properties in tissue was the observation of a nearly linear dependence of the attenuation coefficient on frequency (Pohlman 1939), later verified by Heuter (1948). Hueter also observed that attenuation in muscle tissue was anisotropic due to structural features of striated muscle. The first significant reports of propagation speed and impedance in high-water-content tissues observed that these values did not vary greatly from those of water, and that anisotropic structural features did not significantly affect these parameters (Ludwig 1950).

Researchers had investigated the relationship between macromolecular components of tissue and ultrasound wave propagation to understand ultrasonic absorption in biological tissues. Carstensen et al. (1953) discovered that the absorption and sound speed in blood were due to the amount of protein content of the blood, whether the protein is in solution or contained within cells. Another investigation indicated that a small fraction of the absorption arose due to the cellular organization of the blood (Carstensen and Schwan 1959). Schwan (1959) suggested that the macromolecular components may be responsible for the frequency dependence of acoustical properties in biological media. Pauly and Schwan (1971) showed that approximately two-thirds of the absorption in liver occurred at the macromolecular level, with the remaining one-third being attributed to macroscopic structures in the frequency range of 1–10 MHz. The authors showed that the ultrasonic absorption also depends on *p*H and protein denaturation. The authors observed specific absorption in liver tissue as 0.027 dB/cm per gram of solid component in 100 cm^3 at 1 MHz. Interestingly, the specific absorption in ground, homogenate, sediment, supernatant and nuclei all derived from liver were

0.023, 0.020, 0.027, 0.011 and 0.040 dB/cm per gram solid component in 100 cm^3 at 1 MHz, respectively. Therefore, destruction of the solid tissue resulted only in a moderate change in absorption, indicating that the absorption may be due to the macromolecules rather than the structure of the solid tissue.

Researchers observed variations in absorption by approximately an order of magnitude from one type of substance to another (Pauly and Schwan 1971; Smith and Schwan 1971). Smith and Schwan (1971) measured acoustic absorption of liver cell nuclei and observed that sound absorption per weight percentage of protein content varied from one type of protein to another. In a review article, Wells (1975) suggested that absorption and dispersion in biological materials were due to relaxation processes distributed over a range of frequencies. O'Brien and Dunn (1971, 1972b) suggested that the relaxation processes may be due to solvent-solute interactions and disturbances in H-bonding equilibria. Other researchers investigated the interaction between macromolecules in suspension of erythrocytes (Kremkau et al. 1973). The authors suggested that electrostatic interaction may be important in the sound absorption process. They observed increases in absorption with increasing organization or interaction of biological systems due to chemical and structural relaxations (Kremkau et al. 1973).

Kremkau and Cowgill (1984) measured absorption of several sugars, polysaccharides, amino acids and proteins to determine the importance of molecular weights in biomacromolecular absorption. The authors observed that absorption increases with increasing molecular weight only in the approximate molecular weight range of 500–1,500 daltons. Their results showed that proteins have higher absorption than solutions of amino acids of which they are made, which may be due to higher order structural characteristics present in proteins. In another study, Kremkau and Cowgill (1985) concluded that absorption in globular proteins is insensitive to structural characteristics while in linear proteins it depends upon the amount of $\alpha-$helix content. They suggested that the tertiary structure in the globular protein reduces absorption due to inhibited solvent interactions.

It was established that proteins are largely responsible for absorption in tissues. To understand the underlying mechanism, researchers studied the solutions of this chemical species, of their components and of somewhat related chemical species. O'Brien and Dunn (1972a) investigated propagation of ultrasound through solutions of biological polymers as the first step to understand ultrasonic propagation through tissue microstructure. Specifically, researchers have investigated the absorption in various chemical species such as amino acids, polypeptides, proteins, carbohydrates, bases, nucleotides and nucleosides, nucleic acids and lipids (Dunn and O'Brien 1978).

It was hypothesized that biological tissues act as a composite material whose ultrasonic propagation is mainly governed by the acoustic properties of collagen and globular proteins (Goss et al. 1980a). Pohlhammer and O'Brien (1980) compared ultrasonic attenuation and speed to the concentration of water, collagen, proteins, and fat, given in wet weight percent. Their study concluded that ultrasonic propagation properties of tissue are, indeed, functions of the constituent's concentrations. Water is the most abundant tissue constituent, making up as much as 70–80 % of

many tissues. The water concentration is nonuniformly distributed throughout the body such that adipose tissue and blood are about 10 and 83 % water, respectively. The ultrasonic absorption in water at 37 °C is given by Pinkerton (1949)

$$\alpha = 15.7 \times 10^{-17} f^2, \tag{2.1}$$

where f is the frequency in Hz, and α is the absorption coefficient in Np/cm. The ultrasonic attenuation coefficients in tissues were characterized according to their water concentration given by Goss (1978)

$$\alpha = 9 \times 10^{-12} f W^{-0.74}, \tag{2.2}$$

where W is the water concentration. Using a least squares linear regression, a power function relationship between the ultrasonic attenuation in the 1–10 MHz range and the wet weight percentage of collagen in a tissue was developed (O'Brien 1977a). To the first approximation this yielded

$$\alpha = 0.11 C^{0.51}, \tag{2.3}$$

where C is the wet weight percentage of collagen. Similarly, the authors derived the relationship between ultrasonic speed and collagen concentration given by

$$v = 1588 + 32 \ln C, \tag{2.4}$$

where v is the speed in m/s (O'Brien 1977a).

Collagen plays an important role in the acoustical properties of tissues due to its high tensile strength and it exhibits a wide range of acoustical properties from those of the other common tissue constituents (Pohlhammer and O'Brien 1980). Collagenous fibers exhibit a static elastic modulus approximately 1,000 times higher than other tissues (Fields and Dunn 1973). Because ultrasonic speed is proportional to the square of the elastic modulus, the ultrasonic speed would be significantly greater than other tissue constituents. Due to a higher elastic modulus, collagen is hypothesized to be responsible for much reflection and scattering of ultrasound. Fields and Dunn (1973) suggested that collagen is largely responsible for the echographic visualizability of soft tissues. Other investigators have shown in excised, unfixed breast tissue that fat yields the lowest attenuation and lowest velocity compared to all other surrounding tissue (Greenleaf et al. 1975, 1976). They observed that normal parenchymal breast tissue exhibited relatively high attenuation and moderately high velocity, infiltrating medullary carcinoma exhibited an attenuation between fat and normal breast tissue and high velocity, and connective tissue associated with muscle boundaries of a scirrhous carcinoma clearly exhibited the highest attenuation and velocity. These results clearly infer a relationship between increasing structural protein concentration and increasing ultrasonic speed and attenuation.

Several studies of the relationship between attenuation and collagen concentration in infarcted tissues have been conducted. A quantitative study of the attenuation in normal and infarcted canine myocardium, which was made around two months after the infarct and over the frequency range of 2–10 MHz, indicated

that attenuation increased in the infarcted tissue (Yuhas et al. 1976; Mimbs et al. 1977). O'Brien (1977b) observed that the attenuation in most soft tissue appears to be an increasing function of the collagen content. In another study, O'Donnell et al. (1979) observed a direct correlation between attenuation and collagen concentration. The authors measured frequency-dependent attenuation in the frequency range of 2–11 MHz with respect to collagen content in hearts from normal dogs and in hearts from dogs subjected to ischemic injury by coronary occlusion. The authors detected elevated attenuation in regions of myocardial infarction. The results clearly suggest a correlation between increases in attenuation and increases in collagen in infarcted tissue. Other investigators measured ultrasonic attenuation and sound speed in four different types of tissue elements present in acute myocardial infarction using an acoustic microscope in the frequency range 100–200 MHz (Saijo et al. 1997). The authors measured very low attenuation and sound speed of degenerated myocardium compared with normal myocardium. Furthermore, attenuation and sound speed were very high in fibrotic tissue. From the results, it was suggested that the ultrasonic properties of acute myocardial infarction were due to density, intra- and intercellular structure and bulk elasticity of the tissue element.

O'Brien et al. (1981) characterized cutaneous wound tissue using a 100-MHz scanning laser acoustic microscope. Results of this study indicated that there was an increase in sound speed and attenuation with an increase in the age of the scar tissue. The authors suggested that the increase in the acoustical parameters was caused by both increases in collagen concentration and the changes in nature of the collagen. In another study, researchers documented the normal progression of wound maturation in a canine model using tensile strength measurements, light microscopy, collagen biochemistry and acoustical properties (Olerud et al. 1987). The authors observed a strong correlation between ultrasound speed and attenuation with tissue collagen content [$r = 0.80$ and $r = 0.56$, respectively ($p < 0.001$)]. They also found that ultrasonic speed and attenuation were inversely correlated with tissue water content [$r = -0.57$ and $r = -0.73$, respectively ($p < 0.001$)]. The tensile strength was also correlated significantly with ultrasonic speed and attenuation [$r = 0.90$ and $r = 0.58$, respectively ($p < 0.001$)].

Fat or lipid is a tissue which is almost water free. Generally, at least 10 % of the body weight of the normal mammal is due to lipid. The attenuation in fat is similar to most soft tissue except collagen-high tissues. Ultrasonic speed in fat is approximately 50–100 m/s less than most other tissues, and there is evidence to suggest that sound speed in subcutaneous fat, in particular, is as much as 300–600 m/s lower (O'Brien et al. 1981). Hammes and Roberts (1970), in a study undertaken to examine membrane models, observed excess attenuation only in the presence of the phospholipids in the frequency range of 10–165 MHz at a temperature of 25 °C. The authors postulated four main classes of mechanisms by which ultrasonic energy interacts with phospholipids dispersions: (1) liposomal aggregation, (2) breaking the reforming liposomes, (3) intraliposomal conformational changes and (4) liposome hydration sphere equilibria. Greenleaf and co-workers showed that in excised, unfixed specimens, fat yields the lowest attenuation and lowest sound speed of any of the breast tissues (Greenleaf et al. 1975, 1976). Kossoff et al. (1973) found that

the speed of sound in post-menopausal fatty breast tissue was 7 % lower than that in pre-menopausal breast tissue, with the difference being attributed to a proliferation of fat that occurs as the glandular tissue deteriorates during and following menopause. Thus, these authors suggested that it was possible to distinguish between different states of the breast as well as to identify various benign and malignant conditions by measuring the ultrasonic speed through the tissue.

In fatty liver, fat invades the hepatocytes causing them to balloon which are distributed throughout the organ. Pohlhammer and O'Brien (1980) hypothesized that due to lower ultrasonic speed of fat, these droplets may cause a significant amount of scattering, thereby causing an increase in attenuation with increases in fat content in the liver. Bamber et al. (1981) observed increased attenuation and backscattering with increasing fat content in livers. The authors observed decreased speed of sound with increasing fat content (Bamber and Hill 1981). Other investigators studied the effects of increasing fat in a rat liver on ultrasonic propagation properties using a scanning laser acoustic microscope at 100 MHz (O'Brien et al. 1988). The authors observed that as hepatic lipid increased, ultrasonic attenuation at 100 MHz increased temporally from a normal range of 12–14 dB/mm to a maximum of 54 dB/mm and ultrasonic speed decreased from a normal rage of 1,553–1,584 m/s to a minimum of 1,507 m/s. Thus, quantitative ultrasound (QUS) techniques have been used to quantify properties of the liver in both in vitro and in vivo studies (Bamber and Hill 1981; Fei and Shung 1985; Wear et al. 1995). Researchers have examined the use of attenuation and backscatter coefficients to monitor the stages of the liver remodeling in mice (Guimond et al. 2007; Gaitini et al. 2004). Lu and co-workers demonstrated that the backscatter coefficient and attenuation in patients with diffuse liver disease were higher than in patients with healthy livers (Lu et al. 1999). Suzuki and co-workers observed that the ultrasonic attenuation depends on fatty infiltration of the liver and to a lesser extent on fibrosis (Suzuki et al. 1992).

Another method or ultrasound imaging mode that has been developed to image and quantify sound speed and attenuation is ultrasound computed tomography. The concept of ultrasound time-of-flight computed tomography was first introduced by Greenleaf et al. (1974, 1975). Glover (1977) constructed a two-dimensional velocity distribution in tomographic slices transaxial to the breast from transmission time-of-flight projections with an objective to detect malignant and benign lesions. Dines and Kak (1979) constructed ultrasound attenuation tomograms from formalin-fixed dog heart using various attenuation estimation algorithms. Carson et al. (1981) observed that carcinoma tissues appeared as a bright circular mass of sound speed 1,531 m/s compared to fatty background sound speed of 1,445 m/s in a sound speed tomogram. Greenleaf and Bahn (1981) observed low velocity of 1,400–1,450 m/s in the subcutaneous zone compared to 1,500–1,520 m/s in cysts. They observed that extremely fibrous or schirrous carcinomas tended to have high sound speeds of 1,530 m/s (Greenleaf and Bahn 1981).

Several commercial ultrasound tomography imaging systems are available today (Jeong et al. 2005; Duric et al. 2005; Johnson et al. 2007; Li et al. 2008). Researchers have used a spectral target detection method based on a constrained

energy minimization technique to construct attenuation tomograms and developed a High Resolution Ultrasonic Transmission Tomography (HUTT) system (Jeong et al. 2005). Researchers at the Karmanos Cancer Institute developed a Computerized Ultrasound Risk Evaluation (CURE) device to record reflected, transmitted and diffracted ultrasound signals from the breast to construct sound speed and attenuation tomograms (Duric et al. 2005, 2007). The CURE device operates at a center frequency of 1.5 MHz with 256 transducer elements with a minimum detectable sound speed of 5 m/s. The device has a spatial resolution of 4 mm in sound speed and attenuation tomograms (Duric et al. 2007). The CURE device estimated the sound speeds of fatty and glandular tissues as $1,409 \pm 17$ m/s and $1,472 \pm 37$ m/s , respectively and 75 % of masses >1 cm in size were detected by a combination of reflection and transmission images (Duric et al. 2007). Li et al. (2008) used bent-ray time-of-flight ultrasound tomography to reconstruct sound speed and complex energy ratio to construct attenuation tomograms. Johnson and co-workers used inverse scattering algorithms assuming propagation in fluid media to construct sound speed and attenuation tomograms (Johnson et al. 2007). Unlike previous approaches to ultrasound tomography, the inverse scattering techniques accounted for diffraction, refraction, and multiple scattering effects.

Several researchers have provided comprehensive compilations of available data for the acoustical properties of tissues such as sound speed and attenuation (Goldman and Hueter 1956; Chivers and Parry 1978; Goss et al. 1978, 1980b). The experimental results presented by numerous researchers suggest that ultrasound absorption depends on the macromolecular constituents of tissues. According to the research conducted by numerous researchers, ultrasonic absorption is attributed mainly to the relaxation processes. Nevertheless, more research is necessary to explicitly understand the variation of sound speed and attenuation with tissue properties.

2.3 Quantitative Backscattered Ultrasound Analyses

Conventional B-mode images are derived from backscattered radio frequency (RF) echo signals. The RF echoes are created by reflections from interfaces between acoustically different regions (macrostructure) and by coherent and incoherent scattering from tissue microstructures. Those echo signals contain frequency-dependent information about the smaller scale tissue structures (< wavelength). B-mode image processing hides the frequency-dependent information available in the RF echoes. Conventional B-mode images display large-scale structures (> wavelength) but, to display and quantify smaller-scale structures, the frequency-dependent information must be utilized.

Frequency-dependent scattering from small structures ($\approx$ wavelength) has been used to extract information about properties of different materials in addition to its investigation in medical imaging. Laser scattering has been used to examine glass

and polymer structures (Miyazaki 1974), and neutron scattering has been used to measure molecular bond lengths (Egelstaff et al. 1975). In acoustics, low-frequency sound (<1 kHz) has been used to measure the size and distribution of turbulence in the atmosphere (Wilson et al. 1999).

The RF echoes backscattered from biological tissues contain information about the microstructural properties of the tissues. Preliminary attempts to relate QUS scatterer property estimates to tissue microstructure identified from optical microscope images of the same tissues has met with success. The backscattered signal is a superposition of wavelets scattered from numerous small structures confined within the volume of insonified tissue. The frequency-dependent backscattered signal depends on the average tissue properties (size, shape, number, compressibility, density) of the scatterers within the insonified region relative to the compressibility and density of the medium surrounding the scatterers. The backscattered signal is, therefore, modeled as that resulting from a statistical distribution of scatterers.

The goal of QUS is to estimate parameters, such as effective scatterer diameter (ESD), effective acoustic concentration (EAC), number density and attenuation, from backscattered data from tissues, and associate these parameter values with specific tissue structures. QUS images of scatterer parameters, like ESD and EAC, have been constructed for test phantoms (Insana and Hall 1990) and tissues (Insana et al. 1993). The most simple models that can be used to parameterize the backscattered power spectrum are fitting a line to the spectra and estimating the spectral slope, mid-band fit and spectral intercept (Lizzi et al. 1983). However, the backscattered power spectrum, if modeled correctly, can lead to better QUS estimates of specific scatterer properties.

The ESD, EAC, and number density are values that can be related to microscopic optical histological evaluation. Relating ultrasound backscatter measurements to optical microscope images has been conducted for a variety of tissues (Waag et al. 1983). Specifically, estimates of ESD have been related to the average size of cellular structures in murine models of mammary carcinoma and subcutaneous sarcomas as estimated from their optical microscope images (Oelze et al. 2004). Volume representations from histological sections of scattering tissues can be constructed that are hypothesized to be able to identify the size and distribution of possible scattering sources. The significance of the approach is threefold: (1) QUS estimates can be compared with optical histology findings (validation of the model truth), (2) better models then can be constructed based on comparisons with optical histology and (3) improvement in modeling based on optical histology can increase ability of QUS to diagnose disease.

There have been notable QUS successes. Acoustic scattering theories for biological tissues assume that the tissues can be modeled as either discretely or continuously varying distributions of mass density and bulk compressibility (Insana and Brown 1993). Scattering occurs when an acoustic wave propagates across a region that has local variations in density and/or compressibility. Scattering from simple shapes (spheres and cylinders) has been solved analytically including the effects of shear (Faran 1951). If the scatterers size is comparable to

or smaller than the wavelength and the relative impedance mismatch between scatterer and background is small, then scattering may be modeled using the Born approximation by a spatial autocorrelation function (SAF) (Insana and Hall 1990; Lizzi et al. 1987; Chen 1994).

QUS backscattering techniques have been successfully used to characterize different aspects of tissue microstructures. Noteworthy are the pioneering works that demonstrated theoretically and experimentally the ability to ultrasonically quantify ocular, liver, prostate, renal and cardiac tissues (Miller et al. 1983; Lizzi et al. 1983; Insana et al. 1991).

Feleppa et al. (1986) found that the ESD in ocular tumors was a strong indicator of malignancy. Larger scatterer sizes were observed in malignant tumors when compared with surrounding normal tissues. EAC was also integral to diagnostically distinguishing between ambiguous cases (Lizzi et al. 1987). Feleppa et al. (1996) and Balaji et al. (2002) also demonstrated that QUS parameters provided greater diagnostic accuracy in prostate-cancer detection and lesion localization than all other noninvasive techniques combined.

QUS scattering studies in renal tissues found that changes in the scattering strength (EAC) were responsible for the anisotropy of backscatter and not changes in ESD (Insana et al. 1991) and was, thus, an important parameter for characterizing the anisotropy of backscatter in tissues. The glomeruli ($\approx 200\ \mu$m) and afferent and efferent arterioles ($\approx 50\ \mu$m) were identified as the principal structures responsible for scattering. ESD and sound speed were the most stable QUS parameters for characterizing the tissues. These early studies were the basis of investigations into the ability of QUS images using the scatterer properties to detect changes in renal microanatomy (Insana et al. 1992, 1993, 1995; Garra et al. 1994; Hall et al. 1996). QUS imaging techniques were demonstrated to be capable of differentiating among conditions that caused increased cortical echogenicity and structural changes like glomerular hypertrophy, and QUS measurements agreed well with measurements of those structures in biopsy samples.

For almost 30 years, Coleman and colleagues (Coleman and Lizzi 1983; Coleman et al. 1987, 1990, 1991, 2004; Silverman et al 2001, 2003) strived to develop QUS techniques to diagnose/classify primary malignant melanoma of the choriod and ciliary body to preserve vision without increasing the risk to the patient's life. Earlier, they showed that backscatter properties were correlated with survival in patients with uveal malignant melanoma (Coleman et al 1990, 1991). More recently (Coleman et al. 2004), they successfully demonstrated that QUS parameters of extravascular matrix patterns (EMP) correlated with histologic EMP patterns to discriminate between lethal and less lethal tumors.

Also, for almost 30 years, cardiac studies investigating the cyclic variation in integrated backscatter (Miller et al. 1983; Tamirisa et al. 2001) have demonstrated that this was a useful measure of cardiac function and viability. This work successfully identified the extracellular matrix (Hall et al. 2000) and myocytes (Landini and Santarelli 1995; Recchia et al. 1995) to be the dominant sources of scattering in the heart.

In addition, QUS frequency-dependent backscatter from tissues has been used to enhance B-mode images (Feleppa et al. 1997; Lizzi et al. 1997; Golub et al. 1993; Zagzebski et al. 1993; Topp et al. 2001). Different tissue regions with different scattering properties had their respective, possibly unique, slope and intercept parameters extracted from the scattered power spectrum. Enhanced images were formed by colored pixels in an image corresponding to the local slope and intercept parameters of the power spectrum (Feleppa et al. 1997; Lizzi et al. 1997). The goal of these studies was to use the enhanced QUS images to differentiate between diseased and healthy tissues.

Estimating the number of scatterers per unit volume has also been investigated using a variety of approaches. Wear et al. (1997), Dumane and Shankar (2001) and Shankar (2000) have shown that when the number density of scatterers was small (< 2/ resolution cell), the number of scatterers could be estimated using backscattered envelope statistics. Using fractional order moments of the backscattered envelope (Dutt and Greenleaf 1995), number density could be estimated for scatterer number densities up to 10/resolution cell. The estimates of scatterer number density and EAC could then be used to extract the relative impedance difference between the scatterers and background.

Another example of successful QUS is the work of Donohue and colleagues (Gefen et al. 2003; Varghese and Donohue 1993; Huang et al. 2000) using the generalized spectrum to classify breast tumors. Their results demonstrated that computer-generated features of the RF echo data operated with a true-positive fraction of 100 % and a false-positive fraction of 32 % suggesting the potential for avoiding biopsy of benign breast lesions.

Numerous investigators have pursued QUS breast-imaging techniques with promising results. D'Astous and Foster (1986) found that the attenuation coefficient and its frequency dependence were different for infiltrating ductal cancer (IDC), parenchyma, and fat (3–8 MHz) and those differences increased (due to higher frequency dependence of scattering in IDC) with increasing frequency. They also found that the backscatter coefficient (BSC) for fat and IDC was about the same but was beginning to separate near the upper frequency limit. The BSC for parenchyma was about an order of magnitude above those of fat and IDC, and also exhibited higher frequency dependence. They also found that a two-parameter analysis (attenuation and BSC) was sufficient to separate the three distinct tissue types they studied.

Landini et al. (1987) measured relative backscatter and found similar results to those reported by D'Astous and Foster. A significant difference was that Landini et al. separated fatty tissues into subcategories of fatty and fibro-fatty and found that the backscatter for fatty tissue was between that of scirrhosis carcinoma and medullary carcinoma (4–14 MHz). More significantly, they estimated the correlation functions for five breast-tissue types (the four above plus fibrosis) and found distinct correlation functions (analogous to the ESDs) for each tissue type.

Mortensen et al. (1996) used a feature set consisting of sound speed, attenuation and backscatter parameters to classify in vitro breast-tissue samples as either normal, benign, or malignant with a variety of classifiers. Their best performance,

obtained using an artificial neural network, achieved a diagnostic accuracy of about 93 % even though their data acquisition system did not provide image guidance for ROI selection and operated at relatively low frequencies (3–8 MHz). Their diagnostic accuracy far exceeded the 0.729 found by Stavros et al. (1995) for standard clinical sonography.

Insana et al. (1995) used QUS techniques to follow renal vascular changes in anesthetized dogs during local intra-arterial infusion of a potent vasoconstrictor, endothelin-1 (ET-l). The authors analyzed the backscatter spectra in the frequency range of 5–15 MHz to estimate scatterer size. They observed changes in scatterer size with changes in renal hemodynamics, and increase in attenuation with increasing ET-1 concentration. The authors verified the changes in hemodynamics using Doppler techniques. Insana used a transverse isotropic correlation function to predict backscattering from kidney microstructure (Insana 1995). The author suggested that by analyzing different frequency regimes of the backscatter, structure of different sizes, number densities and scattering strength could be characterized.

Mamou and co-workers used high-frequency ultrasound to estimate different QUS parameters for detecting cancer in excised lymph nodes (Mamou et al. 2011). The authors estimated ESD, EAC, intercept and slope by analyzing the backscatter coefficient from lymph nodes. They used Nakagami and homodyned-K distributions to estimate another four parameters by analyzing the statistics of the envelope of the backscatter signal. The authors obtained a specificity and sensitivity of 95 % by combining ESD and envelope parameters to detect small metastatic foci in dissected lymph nodes.

Recently, cell pellets made of Chinese hamster ovary (CHO) cells were used to understand ultrasound wave propagation in biological media (Teisseire et al. 2010). An analytical scattering model was used to predict the sound speed in nucleus and cytoplasm as 1,802 m/s and 1,952 m/s, respectively, at a low number density of 1.3×10^6 cells/mL. They used a concentric sphere scattering model to predict the scattering in nucleus and cytoplasm. In a subsequent study, Han et al. (2011) estimated the attenuation in CHO cell pellets at low concentration as $0.021f^{1.6}$ dB/cm using a power law fit in the frequency range of 20–100 MHz. The authors observed different attenuation slopes as the concentration of cells increased in the cell pellets. With better attenuation compensation and improved data-processing strategies and scattering models from those used by Teisseire et al. (2010), Han et al. (2011) estimated the sound speed in nucleus and cytoplasm around 1,600 m/s and 1,550 m/s, respectively, at the lower number densities in CHO cell pellets.

QUS techniques relying on normalized backscattered power spectra have been used to assess apoptosis and necrosis of tumors undergoing both thermal therapy and chemotherapy (Czarnota et al. 1999; Kolios et al. 2002; Banihashemi et al. 2008; Vlad et al. 2009). Czarnota and coworkers used high-frequency (40 MHz) ultrasound to quantify the changes in the backscatter amplitude from cells in vitro undergoing apoptosis due to anticancer agents, apoptosis in tissues ex vivo and

apoptosis in tumors in live animals (Czarnota et al. 1999). They observed large changes in backscatter amplitude from regions of cell death compared to surrounding viable tissues. Kolios et al. (2002) estimated spectral slope and midband fit parameters from backscattered power spectra to monitor apoptosis in in vitro and in vivo experiments due to chemotherapy. The authors observed increases in spectral slope and midband fit with respect to time after drug exposure. Banihashemi et al. (2008) also observed increases in backscattered power with respect to time after application of photodynamic therapy. The authors correlated the QUS parameters to apoptosis and histologic variations in cell nuclear size and observed changes in spectral slope with respect to changes in nuclear size. Similarly, Vlad et al. (2009) observed changes in backscatter spectral parameters due to changes in cellular microstructure with application of radiotherapy. These results clearly suggest that QUS imaging can be used to monitor therapy response.

All of the above work aimed at quantifying backscattered signals through system-independent techniques to quantify the backcattered power. Other investigators have implemented different approaches to 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. Although their patient population was small, they only used 5 and 7.5 MHz transducers, and 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 100 % sensitivity for cancer. Using similar data acquisition, image texture parameters and an artificial neural network, Chen et al. (1999) obtained a diagnostic accuracy of 95 % and with the sensitivity set at 98 %, they achieved a specificity of 93 %, positive predictive value of 89 % and negative predictive value of 99 %. Although very encouraging, these results are nonetheless system dependent. Nevertheless, their success demonstrates that measures of texture statistics (including co-occurrence matrix, run length, etc.) have merit for differentiating among breast diseases

The obvious step to translate QUS imaging to the clinics is to test the feasibility of estimated parameters to be reproducible across different transducers and systems. Several studies have been conducted to compare QUS parameters by different systems and users from the same sample. Ten laboratories participated in an interlaboratory study to estimate backscatter coefficients from tissue–mimicking phantoms using individual laboratory's systems, operators and techniques (Madsen et al. 1999). The study found considerable differences in backscatter coefficient estimates between laboratories, which may be related to the accuracy of the techniques used by each group. A better agreement was observed in a subsequent interlaboratory study to compare backscatter coefficients from tissue–mimicking phantoms (Wear et al. 2005). In this study, the estimated backscatter coefficients were compared with theoretical values. Another interlaboratory study of backscatter coefficients from tissue–mimicking phantoms, where glass beads were used as scatterers, was conducted between two laboratories (Anderson et al. 2010). The main aim was to investigate the interlaboratory comparison of Faran's theoretical model (Faran 1951) to predict backscatter coefficients in the frequency range 1–12 MHz from

glass spheres embedded in a uniform agar-based background. The results of the study demonstrated good agreement between the two laboratories and the theoretical model except for one of the tissue–mimicking phantoms (Anderson et al. 2010). Further interlaboratory comparison of backscatter coefficients from tissue-mimicking phantoms with glass beads as scatterers were conducted using four different clinical array-based imaging systems (Nam et al. 2012a, b). Another interlaboratory study was conducted to develop tissue-mimicking phantoms with weak scatterers and compare theoretical prediction of backscatter coefficient with experimental results in the frequency range of 1–13 MHz (King et al. 2010). The study concluded with good agreement between the two laboratory experimental results and theoretical predictions of backscatter coefficients. The scattering properties of these weakly scattering phantoms represent biological tissue better than glass bead phantoms (King et al. 2010). Good agreement was found between the laboratories and theoretical predictions demonstrating that these QUS parameters based on the backscatter coefficients from different scattering media are reproducible and can be system and operator independent.

Interlaboratory studies to estimate the backscatter coefficient from in vivo spontaneous rat mammary tumors (fibroadenoma and carcinoma) acquired by different research groups using three clinical array systems and a single-element laboratory scanner system were conducted (Wirtzfeld et al. 2010). The results were encouraging from this first in vivo study to compare QUS parameter estimates by different laboratories and systems scanning the same tumor in vivo. Better agreement in backscatter coefficients was observed from in vivo spontaneous rat mammary tumors in the second joint study by the same group of laboratories (Wirtzfeld et al. 2013). In this study the researchers used functional ANOVA to compare the frequency dependence of the backscatter coefficients across different systems (Wirtzfeld et al. 2013).

The successes, outlined above, in applying QUS techniques to improve diagnosis have not yet led to broad application. Part of the reason is that the techniques were either too computationally intensive for existing hardware, or not extensive enough to be robust for everyday clinical use. Furthermore, correcting effects of attenuation have been problematic to date. However, recent progress has been made in developing algorithms to accurately predict the attenuation in tissues. Therefore, the main roadblocks to clinical implementation have been largely overcome in recent years. The success to date places QUS techniques on the cusp of broad clinical applicability.

2.4 Conclusion

The QUS technology and successes outlined in this chapter will form a new imaging capability that will be used as an optional mode to augment standard B-mode imaging, analogous to the use of ultrasound-based flow estimation. The successes outlined in this chapter demonstrate that the QUS techniques can

provide new sources of contrast for improved image diagnostics. We do not expect that QUS will solve all of the limitations of current imaging modalities. However, the new information provided through QUS will likely improve performance of diagnostic ultrasound. We anticipate that QUS information will be part of a multimode analysis that augments B-mode imaging, (e.g., spectral Doppler, color-flow imaging, elasticity imaging, etc.). Just as modalities such as MRI can acquire image information based on different tissue properties, we believe that ultrasound machines will provide useful diagnostic information when QUS parameters are displayed to augment the time-honored B-mode image. Transducer technology, beamforming flexibility, and information-processing capacity are now emerging that will enable the development of this new generation of machines. The history of successes for QUS to detect, quantify and diagnose a host of different diseases and tissue conditions suggests that QUS techniques have an important role to fill in ultrasound medical diagnostics. Interlaboratory studies have demonstrated that these techniques can be system and user independent. Therefore, future clinical machines will likely include different QUS imaging modes.

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