

# Quantitative Ultrasound and the Management of Osteoporosis

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*Quantitative ultrasound is a clinically validated, low-cost, portable, nonionizing alternative to traditional X-ray methods for managing osteoporosis.*

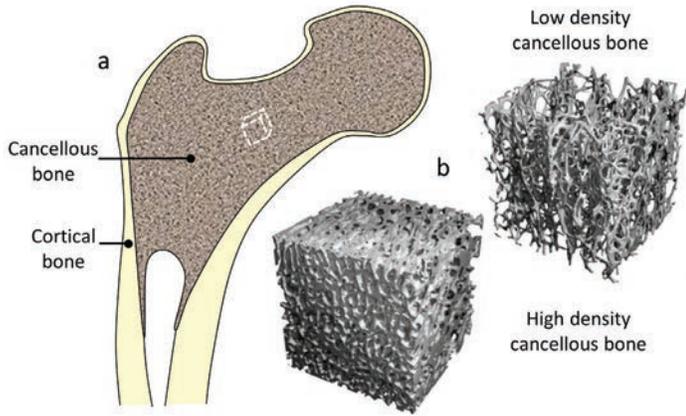
## Osteoporosis, Bone Structure, and X-ray Diagnostic Methods

Do you know somebody who suffers from osteoporosis? There is a good chance that you do. An estimated 54 million adults in the United States are affected by osteoporosis or low bone mass (Wright et al., 2014). Osteoporosis, which means “porous bone,” is a systemic skeletal disease characterized by decreased bone density and increased fracture risk. Globally, osteoporosis is responsible for 9 million fractures per year (Johnell and Kanis, 2006). Medical costs for the treatment of osteoporosis in the United States are projected to be \$25 billion per year by 2025 (Burge et al., 2007).

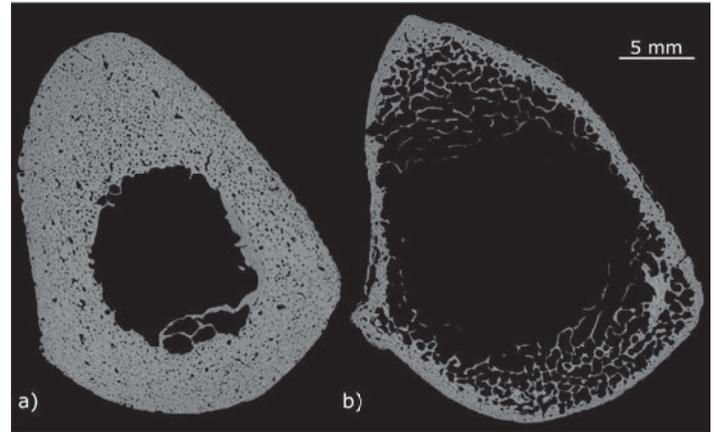
Osteoporosis disproportionately affects postmenopausal women. After menopause, decreased estrogen levels disrupt the normal process of bone turnover in which specialized cells called osteoclasts remove old bone tissue while other specialized cells called osteoblasts build new bone tissue. When osteoclast activity exceeds osteoblast activity, net bone loss occurs. Fortunately, drugs are available to treat this condition. It is estimated that 1 in 2 women and 1 in 4 men over the age of 50 will break a bone due to osteoporosis (National Osteoporosis Foundation, 2018).

Bones contain two main types of tissue (**Figures 1** and **2**). Cancellous bone (also called trabecular bone) is a lightweight, highly porous material located toward the inner regions of bones (**Figure 1**). Cortical bone is dense material that forms the outer shell (cortex) of bones. Both tissues consist of an organic phase (mainly collagen) and a mineral phase (mainly hydroxyapatite). The diagnosis of osteoporosis is often based on X-ray measurements of bone mineral density (BMD; **Figure 2**; see **Table 1** for a list of abbreviations), which quantifies the concentration of hydroxyapatite.

The most common diagnostic technique for osteoporosis is a two-dimensional technique called dual-energy X-ray absorptiometry (DXA). DXA measurements performed at the hip and spine, common locations for osteoporotic fractures, are considered the “gold-standard” method for diagnosing osteoporosis. However, DXA measurements at these central skeletal locations are inconvenient because they require large, whole body scanners. More portable options include peripheral DXA (pDXA) and peripheral quantitative computed tomography (pQCT) systems, both of which perform X-ray BMD measurements at peripheral skeletal locations such as the leg or forearm. Another option is quantitative ultrasound (QUS).



**Figure 1. a:** Bones consist of two types of tissue: cortical and cancellous. As osteoporosis progresses, the cortical layer becomes thinner and the cancellous bone becomes more porous. **b:** High-resolution X-ray computed tomography images showing low- and high-density specimens of cancellous bone excised from the femur (thigh bone) near the location shown in a.



**Figure 2.** Acoustic impedance images of human cortical bone transverse cross sections from the tibia (long bone of the lower leg) measured at 100 MHz. **a:** Healthy specimen; **b:** late-stage osteoporotic specimen showing dramatic thinning of cortical bone. See Raum et al., 2008.

## Clinical Ultrasound Devices for Bone Fracture Risk Assessment

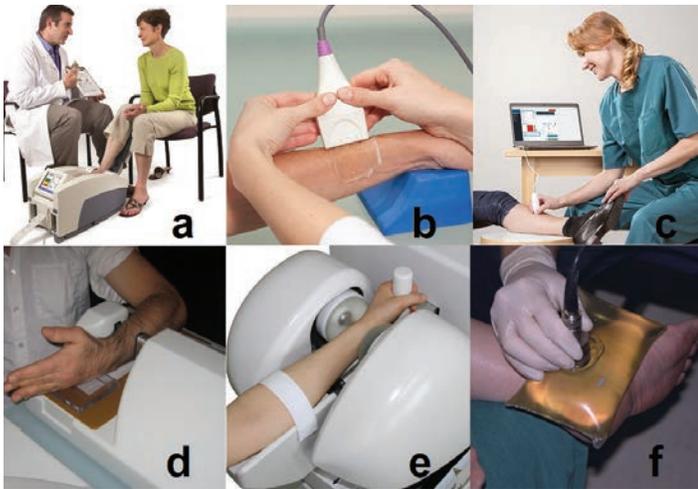
The earliest and best-validated design for a clinical bone ultrasound device uses a broadband ultrasound transducer to transmit an ultrasound beam through the calcaneus (heel bone; **Figure 3a**). A receiving ultrasound transducer is placed on the opposite side of the foot. With this “through-transmission” geometry, measurements of broadband ultra-

sound attenuation (BUA) and speed of sound (SOS) may be performed. Both BUA and SOS have been shown to be highly correlated with calcaneal BMD. Attenuation in bone is far greater than attenuation in soft tissues so attenuation due to soft tissue surrounding the calcaneus has little impact on the measurements. Using a broadband ultrasound transducer allows attenuation to be measured at multiple frequencies (typically, about 300–700 kHz). Attenuation in bone increases with frequency and is usually characterized by the slope of a linear fit to attenuation versus frequency (BUA; see **The Interaction of Ultrasound with Cancellous Bone**). The SOS may be estimated from the time delay between transmitted and received ultrasound pulses.

The initial clinical validation for through-transmission calcaneal ultrasound came from large-scale trials. In a retrospective study of 4,698 women, the association between BUA at the heel and at existing fractures was nearly the same as that between DXA at the heel and at existing fractures (Glüer et al., 1996). In a prospective study of 5,662 women, ultrasonic measurements at the heel (BUA and SOS) predicted the risk of hip fracture in elderly women nearly as well as DXA at the hip (Hans et al., 1996). In a prospective study of 6,189 postmenopausal women, the strength of the association between the BUA at the heel and at the fracture was comparable to that observed with DXA (Bauer et al., 1997). These and subsequent studies represent the foundation for formal recognition of the diagnostic effectiveness of calcaneal ultrasound by professional organizations (Krieg et al., 2008; US Preventive Services Task Force, 2011).

**Table 1.** Abbreviations

Term	Definition
AT	Axial (along the axis of long bones) transmission
BDAT	Bidirectional axial transmission
BMD	Bone mineral density (in $\text{g}/\text{cm}^2$ for projection methods like DXA or $\text{g}/\text{cm}^3$ for volumetric methods like QCT)
BUA	Broadband ultrasound attenuation (in $\text{dB}/\text{MHz}$ )
DXA	Dual-energy X-ray absorptiometry
FAS	First arrival signal
FFGW	Fundamental flexural guided wave
HR	High resolution
HR-pQCT	High-resolution peripheral quantitative computed tomography
nBUA	Normalized (to bone thickness) BUA (in $\text{dB}/\text{cmMHz}$ )
pDXA	Peripheral dual-energy X-ray absorptiometry
pQCT	Peripheral (arms, legs, hands, feet) QCT
QCT	Quantitative computed tomography
QUS	Quantitative ultrasound
SOS	Speed of sound (in $\text{m}/\text{s}$ )
TOF	Time of flight (in $\text{s}$ )



**Figure 3.** Various types of ultrasound systems to measure bone: **a:** General Electric Lunar (Madison, WI) Achilles®; **b:** BeamMed (Petah Tikva, Israel) MiniOmni®; **c:** Bone Index (Kuopio, Finland) Bindex®; **d:** CyberLogic (New York, NY) UltraScan 650®; **e:** Oyo (Kyoto, Japan) LD-100®; **f:** custom backscatter system (Wear and Armstrong, 2001).

Calcaneal ultrasound is currently the most prevalent ultrasound method in the management of osteoporosis. However, because the calcaneus is mostly cancellous bone surrounded by a very thin cortical layer, calcaneal ultrasound does not assess cortical bone strength and therefore gives an incomplete prediction of fracture risk. Other devices have been designed to interrogate cortical bone in addition to, or instead of, cancellous bone. Cortical bone devices often target long bones such as the tibia (long bone of the leg) or radius (long bone of the arm).

Another commercial bone ultrasound device uses two transducers (transmitter and receiver) to measure the SOS along the cortex of a long bone (Figure 3b). In a retrospective study of 254 postmenopausal women, SOS measurements at the forearm, finger, or midfoot demonstrated an ability to discriminate fracture cases from control cases in postmenopausal forearm fracture patients, although the performance was inferior to measurements of the spine and femur BMDs (Knapp et al., 2002).

Another commercial bone ultrasound device applies a single ultrasound transducer placed perpendicular to the leg or arm (Figure 3c). Using pulse-echo ultrasound, the single transducer transmits a pulse and receives the echoes from the outer and inner surfaces of the bone cortex. From the time delay between the two echoes, an index of cortical thickness can be obtained if a value for the cortical SOS is assumed. The method was validated on human tibia samples in vitro

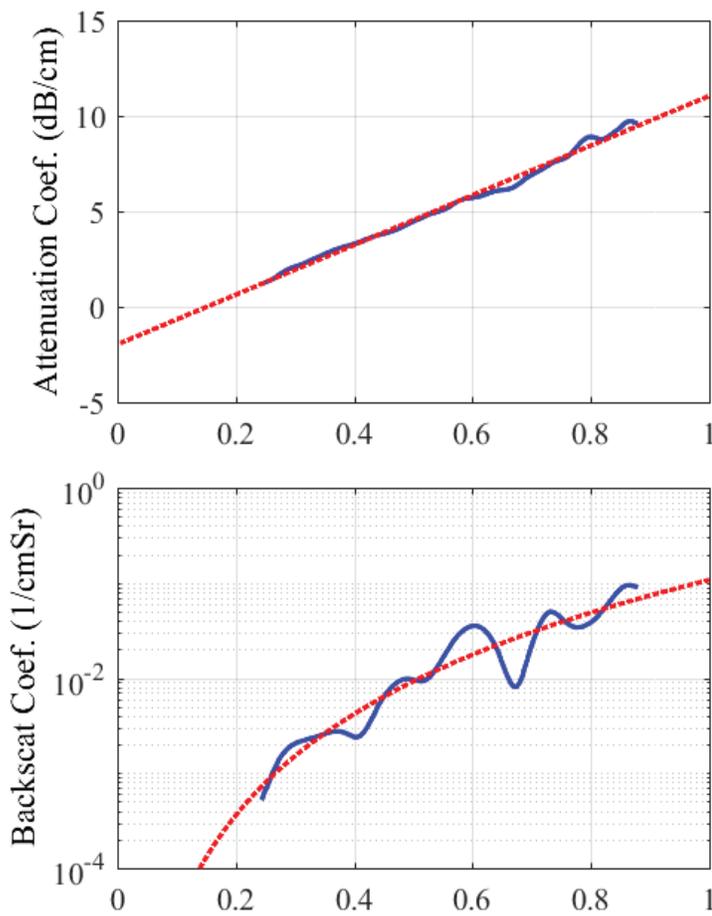
(Wear, 2003) and in a clinical trial involving 572 women for improving the management of patients suspected of having osteoporosis (Karjalainen et al., 2016).

Another design uses a two-transducer through-transmission geometry, like the calcaneus-based devices, but measures the forearm instead of the calcaneus. One implementation uses measurements of time-delay (between transmitted and received signals) parameters to estimate an index of BMD in the radius and has been validated in a clinical trial involving 60 adults for having a high correlation with BMD (Stein et al., 2013; Figure 3d). Another implementation uses measurements of two longitudinal waves predicted by the Biot theory (see **The Interaction of Ultrasound with Cancellous Bone**) that propagate through the radius to estimate bone density and elasticity (Otani et al., 2009) and cortical thickness (Mano et al., 2015) and has been validated in a clinical trial involving 93 adults for having high correlations with BMD and cortical thickness (Breban et al., 2010; Figure 3e).

Another design uses a single transducer in pulse-echo mode to measure scattering from cancellous bone. This approach only requires access from one side of a bone and has accessibility to sites beyond the calcaneus, including the hip and spine. Backscatter from the calcaneus showed a high correlation with the BMD in 10 normal human volunteers (Wear and Garra, 1998) and 47 women (Wear and Armstrong, 2001; Figure 3f). In a retrospective study of 210 postmenopausal women, backscatter from the calcaneus was shown to have a significant association with fractures (Roux et al., 2001). A recent study involving 342 women showed that a backscatter measurement could be acquired from the lumbar spine in vivo and had a moderate correlation with BMD measurement (Conversano et al., 2015)

### The Interaction of Ultrasound with Cancellous Bone

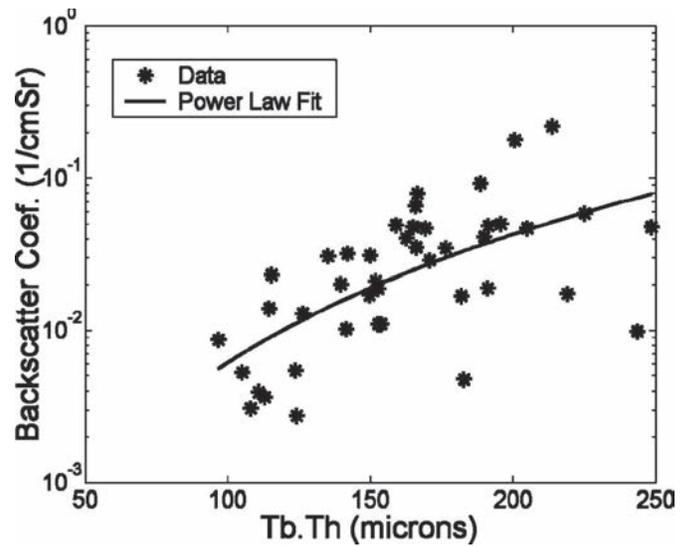
The motivation for the through-transmission calcaneus ultrasound comes from a seminal paper that represents the first report of an age-related decline in BUA in cancellous bone in women (Langton et al., 1984). The first paper to report measurements of BUA and SOS in human volunteers showed that both exhibited strong correlations with BMD measurements (Zagzebski et al., 1991). Another early system extended this design by adding scanning capability to produce images of BUA in vivo (Laugier et al., 1996). These papers led to the development of clinical through-transmission calcaneus-based systems that were used in early large-scale trials mentioned in **Clinical Ultrasound**



**Figure 4.** Attenuation (*top*) and backscatter (*bottom*) coefficients (Coef.) of a cancellous bone sample *in vitro* (*blue curves*). A linear fit is shown for the attenuation coefficient data (*top red dashed line*). The slope of the line is normalized broadband ultrasound attenuation (*nBUA*). A power law fit is shown for the backscatter coefficient data (*bottom red dashed curve*). *cmSr*, centimeter steradians.

**Devices for Bone Fracture Risk Assessment** to provide a foundation for clinical quantitative ultrasound in bone.

Studies involving human calcaneus samples *in vitro* have provided insight into determinants of BUA and SOS. **Figure 4, top**, shows the attenuation coefficient versus frequency for a cancellous bone sample *in vitro*. The slope of a linear fit to these data is called normalized BUA (*nBUA*) and is measured in decibels per centimeter per megahertz (dB/cmMHz). When the thickness of the calcaneus is unknown, as is the case with clinical measurements, the parameter reported is BUA, which is measured in decibels per megahertz (dB/MHz). Mechanical compression studies have indicated that BUA has a strong relationship with the mechanical properties of cancellous bone (Langton et al., 1996). A theoretical model for relationships among the SOS, *nBUA*, and dispersion (frequency-dependent phase velocity) in cancellous bone has been validated in human bone *in vitro* (Wear,

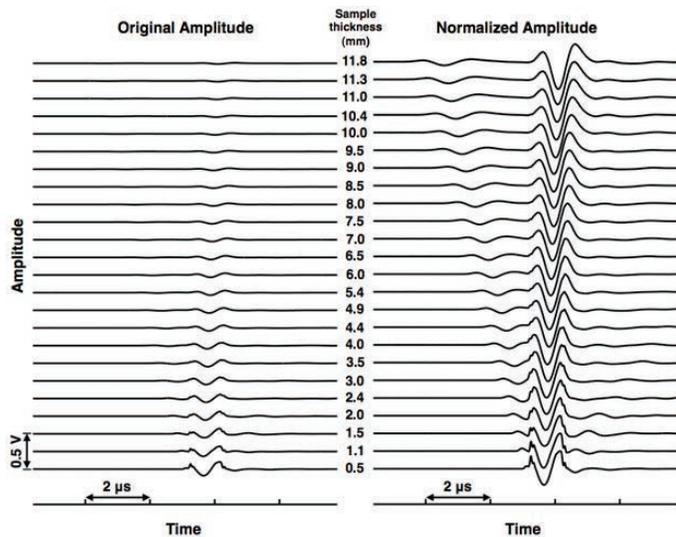


**Figure 5.** Backscatter coefficient versus trabecular thickness (*Tb.Th*) in 43 human calcaneus samples *in vitro*. Reprinted, from Wear and Laib, (2003), with permission, © 2003 IEEE.

2000). BUA and SOS primarily provide information related to bone quantity but also provide some information related to the microarchitecture of cancellous bone (Chaffai et al., 2002). BUA and SOS are sensitive to the volumetric density (Hoffmeister et al., 2000) and collagen and mineral content (Hoffmeister et al., 2002) of cancellous bone.

Measurements of scattering from human calcaneus samples *in vitro* have elucidated mechanisms underlying BUA (because scattering is one source of attenuation) and the clinical scattering findings discussed in **Clinical Ultrasound Devices for Bone Fracture Risk Assessment**. **Figure 4, bottom**, shows the backscatter coefficient versus frequency for a cancellous bone sample *in vitro*. In the clinical frequency range (approximately 300-700 kHz), the backscatter coefficient  $[\eta(f)]$  depends on frequency ( $f$ ) as a power law  $[\eta(f) = Af^n]$  when  $n$  is a little higher than 3 (Wear, 1999; Chaffai et al., 2000). The backscatter coefficient is approximately proportional to the mean trabecular thickness (the width of mineralized tubular structures in cancellous bone; see **Figure 1b**) to the third power (Wear and Laib, 2003; **Figure 5**). Like BUA and SOS, backscatter is sensitive to the volumetric density (Hoffmeister et al., 2000), BMD (Hoffmeister et al., 2006), and collagen and mineral content (Hoffmeister et al., 2002) in cancellous bone. In the clinical frequency range, single scattering is believed to be much stronger than multiple scattering (Wear, 1999; Haiat et al., 2008).

One interesting feature of porous media is that a single longitudinal pressure wave entering a porous sample can generate two longitudinal pressure waves propagating at different velocities (called “fast” waves and “slow” waves). This phenomenon is explained by the Biot theory (Biot, 1956) and



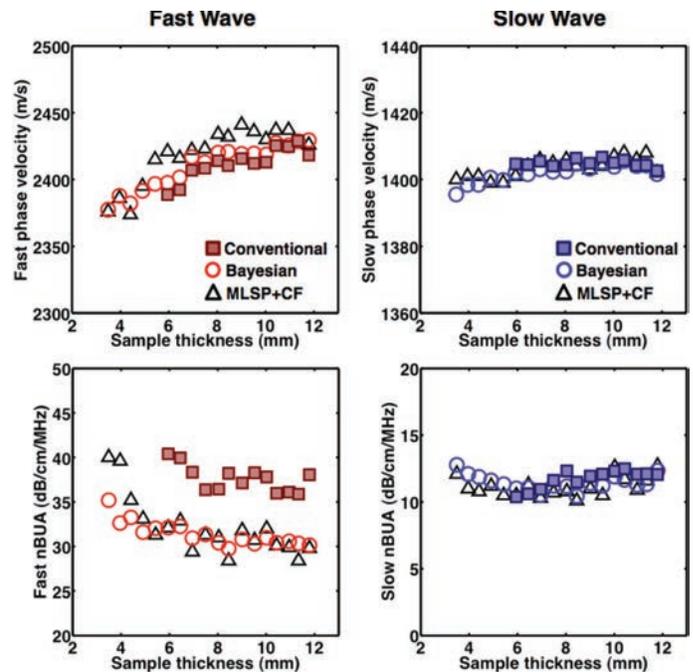
**Figure 6.** Ultrasound signals from through-transmission measurements of cancellous bone sample for thicknesses ranging from 0.5 to 11.8 mm. Signals were obtained by alternately performing through-transmission measurements and shaving approximately 0.5 mm from the bone sample. The normalized amplitude is magnified to show both fast (low-amplitude; left) and slow (high-amplitude; right) waves. For the thickest samples, the fast and slow waves are well separated. For samples thinner than 6 mm, however, fast and slow waves begin to overlap (Groopman et al., 2015).

has been demonstrated in cancellous bone (Williams, 1992; Hosokawa and Otani, 1997; Lee et al., 2003; **Figure 6**). Because fast and slow waves often overlap in both the time and frequency domains, advanced signal-processing methods have been developed to separate them (Groopman et al., 2015; **Figure 7**).

### The Interaction of Ultrasound with Cortical Bone

Calcaneal devices, which target cancellous bone, were introduced about 20 years ago and have since received formal recognition of their clinical effectiveness from professional organizations (Krieg et al., 2008; US Preventive Services Task Force, 2011). Many devices that target cortical bone are newer and still undergoing research and development. Cortical devices aim to measure changes in cortical thickness and porosity, both of which have been shown to be related to fracture risk.

Because it is a projection technique, DXA has limited capability to provide reliable quantitative measurements on cortical bone. High-resolution (HR) pQCT (HR-pQCT)



**Figure 7.** Fast- and slow-wave decomposition of the data from **Figure 6**. Phase velocity (top) and nBUA (bottom) of fast (left) and slow (right) waves are functions of sample thickness. Bayesian and Prony’s (modified least-squares Prony’s plus curve-fitting [MLSP+CF]) methods can recover wave properties at thicknesses below 6 mm even when fast and slow waves overlap and conventional methods fail. Bayesian and Prony’s methods show high agreement with each other and provide plausible extrapolations of properties for thicknesses below 6 mm (Groopman et al., 2015).

provides full three-dimensional information but is expensive and limited to clinical research facilities.

Ultrasound waves transmitted by a source through the skin to a long bone (such as the radius or the tibia) can generate vibrations that propagate in the cortex along the axis of the bone. As they propagate, these guided waves leak energy from the waveguide to the adjacent soft tissue. The leaked energy can be detected using sensors placed on the skin, typically a few centimeters away from the source. So-called axial transmission (AT) methods have been developed to measure these guided waves.

An early approach used point contact transducers with exponential waveguides to measure the speeds of surface and flexural waves at the mid tibia at 100 kHz. Guided waves were used to measure patients with immobilization atrophy (Dzene et al., 1980) and to monitor skeletal demineralization of cosmonauts exposed to microgravity (Tatarinov et al., 1990).

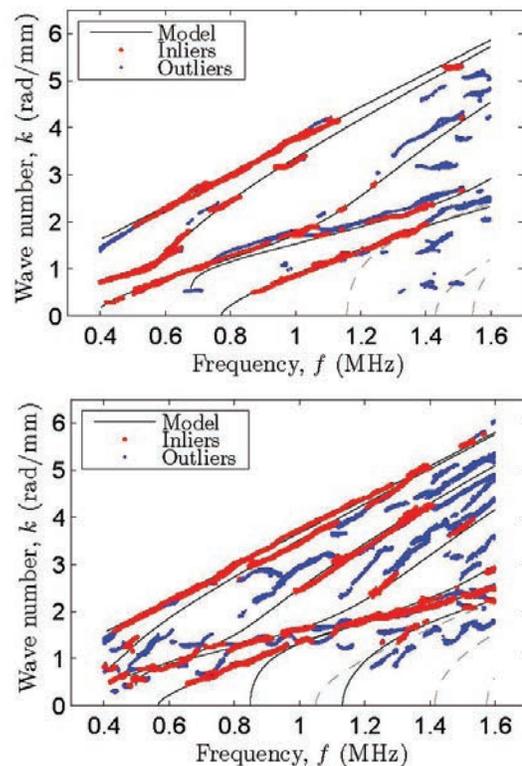
Over the past two decades, the determination of guided modes and identification of cortical bone waveguide characteristics has sparked increased investigation of signal-processing approaches, modeling, and inverse problem solving. At least two cortical devices have appeared on the market and have been tested in clinical studies (Barkmann et al., 2000).

With earlier approaches, a one transmitter-one receiver configuration was implemented in which wave velocity could be computed from the separation distance and the measurement of the time of flight (TOF) between transmitted and received signals. The TOF technique has been used to evaluate the velocity of the first arrival signal (FAS), which is defined as the first component of the signal that emerges from noise. The FAS contains relevant information on the microstructural and material properties (Talmant et al., 2011). However, it cannot be easily predicted by analytical methods and therefore is difficult to infer from waveguide characteristics. FAS is a transient mode, consistent with a lateral longitudinal wave (which propagates at the longitudinal bulk velocity) when the ratio of the cortical thickness to the acoustic wavelength is much greater than 1 or the  $S_0$  Lamb mode for a plate if the acoustic wavelength is not much greater than 1 (Talmant et al., 2011).

FAS velocity evaluation may be improved by making TOF measurements at multiple receiver positions, either by moving the receiver or by using a multielement transducer array. In addition to the FAS, a slower waveform has been isolated and interpreted as a fundamental flexural guided wave (FFGW; equivalent to  $A_0$  Lamb mode for a plate; Nicholson et al., 2002). The dispersion characteristics (frequency-related phase velocity variations) of this mode are very sensitive to cortical thickness (Moilanen et al., 2007).

One AT device uses two frequencies. Measurements at 100 kHz strongly depend on the cortical thickness, whereas measurements at 1 MHz depend mainly on propagation parameters of the bulk longitudinal wave (mass density and stiffness). Researchers claim that dual-frequency AT ultrasound can detect early changes induced by osteoporosis more clearly than can single-frequency AT ultrasound (Sarvazyan et al., 2009).

These analyses of AT signals were restricted to analyzing a single waveform, either the FAS or the FFGW. However, an infinite number of guided waves can exist. Multiple modes contain more information but are more difficult to interpret. Each mode interferes with every other mode, and



**Figure 8.** Optimal matching between the experimental data (dots) and Lamb modes (continuous lines) for an ex vivo (top) and in vivo radius (bottom). Inliers and outliers (i.e., experimental data that are not explained with the free-plate model) are displayed as red and blue dots, respectively. Reprinted from Bochud et al. (2016), with permission.

distinguishing modes or their dispersion curves in recorded signals can be tricky. Researchers have developed an AT technique, bidirectional AT (BDAT), to solve this problem. BDAT uses a one-dimensional linear transducer array to record guided modes that propagate in two opposite directions from two emitting transducer arrays placed on each side of the central receiving array. Combining measurements from two opposite directions automatically compensates for bias on measured wave speeds resulting from the surrounding soft tissues (Moreau et al., 2014).

The BDAT probe is a 1-MHz array adapted to clinical measurements at the one-third distal radius. It consists of 24 receivers surrounded by 2 arrays of 5 emitters each. A matrix response is recorded by repeatedly firing pulses into the bone from each element of the emitting arrays and recording the response at each element of the receiving array. Dispersion curves are obtained by a reconstruction method based on a singular value decomposition combined with a two-dimen-

sional spatiotemporal Fourier transform of the signal received by each element (Minonzio et al., 2010). Background noise can be filtered by choosing the appropriate number of singular values to optimize the signal-to-noise ratio. In addition, BDAT allows visualization of the low-energy modes.

Once dispersion curves are obtained, waveguide characteristics are retrieved through an inversion method, based on a two-dimensional transverse isotropic free-plate model, that allows the concurrent identification of cortical thickness and porosity (**Figure 8**). Site-matched microcomputed tomography images of the bone specimens imaged served as the gold standard to assess the accuracy of thickness and porosity estimates. Excellent agreement was observed for thickness, and relatively good overall agreement was obtained for porosity. In a pilot in vivo study, BDAT could determine cortical thickness nearly as accurately as conventional HR X-ray computed tomography (Vallet et al., 2016).

BDAT is currently under clinical evaluation. In a study including 205 postmenopausal women, including 102 with 1 or more nontraumatic fractures, fracture prediction was significant for hip fractures with cortical thickness and for vertebral fractures with cortical porosity (Minonzio et al., 2017).

### Looking Ahead

DXA remains the primary modality for the management of osteoporosis because it has imaging capability, can target the hip and spine, and has abundant evidence to support clinical utility. However, calcaneal ultrasound has demonstrated comparable performance for fracture risk prediction in clinical trials involving thousands of women. Cortical ultrasound has also demonstrated substantial clinical utility. Moreover, quantitative ultrasound device technology is rapidly evolving, with several new device designs introduced just in the last few years. Because of its established clinical utility, lack of ionizing radiation, low cost, and portability, quantitative ultrasound has a promising future, especially for screening.

### Disclaimer

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## BioSketches



**Keith A. Wear** received his BA in applied physics from the University of California, San Diego, La Jolla, CA. He received his MS and PhD in applied physics from Stanford University, Stanford, CA. He is the acoustics laboratory leader at the Food and Drug Administration, Silver Spring, MD. He is an associate editor of three journals: *The Journal of the Acoustical Society of America*; *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*; and *Ultrasonic Imaging*. He is a fellow of the Acoustical Society of America, the American Institute of Ultrasound in Medicine, and the American Institute for Medical and Biological Engineering.



**Brent K. Hoffmeister** received his BA in physics from Wabash College, Crawfordsville, IN, and his MA and PhD in physics from Washington University, St. Louis, MO. He is a professor of physics and chair of the physics department at Rhodes College, Memphis, TN. He is a member of the Acoustical Society of America and serves on the editorial board of *Ultrasonic Imaging*.



**Pascal Laugier** has a PhD in physical acoustics from the University of Paris, France, and holds a permanent position at the Centre National de la Recherche Scientifique (National Center for Scientific Research; CNRS) as a research director. He is the head of the Biomedical

Imaging Laboratory at Sorbonne Université. With his team, he has been involved for 25 years in sustained research in the field of bone quantitative ultrasound. He developed the first ultrasound bone imaging densitometer that was marketed in the 2000s. Despite this, his sons had a greater admiration for the actor Will Smith who was selling similar portable bone density scanners in the film *The Pursuit of Happyness*.

The ASA's Women in Acoustics Committee was created in 1995 to address the need to foster a supportive atmosphere within the Society and within the scientific community at large, ultimately encouraging women to pursue rewarding and satisfying careers in acoustics.

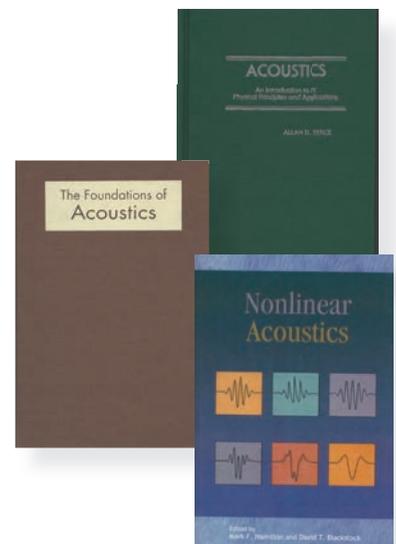
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