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The dependence of time-domain speed-of-sound measurements on center frequency, bandwidth, and transit-time marker in human calcaneus *in vitro*.

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Abstract

Time-domain speed-of-sound (SOS) measurements in calcaneus are effective predictors of osteoporotic fracture risk. High attenuation and dispersion in bone, however, produce severe distortion of transmitted pulses that leads to ambiguity of time-domain SOS measurements. An equation to predict the effects of system parameters (center frequency and bandwidth), algorithm parameters (pulse arrival-time marker) and bone properties (attenuation coefficient and thickness) on time-domain SOS estimates is derived for media with attenuation that varies linearly with frequency. The equation is validated using data from a bone-mimicking phantom and from 30 human calcaneus samples *in vitro*. The data suggest that the effects of dispersion are small compared with the effects of frequency-dependent attenuation. The equation can be used to retroactively compensate data. System-related variations in SOS are shown to decrease as the pulse-arrival-time marker is moved toward the pulse center. Therefore, compared with other time-domain measures of SOS, group velocity exhibits the minimum system dependence.

Keywords

calcaneus; trabecular bone; cancellous bone; velocity; dispersion; osteoporosis

Introduction

Speed of sound (SOS) in calcaneus is very useful for characterization of bone and diagnosis of osteoporosis (Rossman *et al.*, 1989; Tavakoli and Evans, 1991; Zagzebski *et al.*, 1991; Laugier *et al.*, 1993; Njeh *et al.*, 1996; Bouxsien, 1997; Bauer *et al.*, 1997; Laugier *et al.*, 1997; Strelitzki and Evans, 1996; Strelitzki, *et al.*, 1997; Nicholson *et al.*, 1996; Nicholson *et al.*, 1998; Hans *et al.*, 1999; H. Trebacz, and A. Natali, *et al.*, 1999; Hoffmeister *et al.*, 2000; Hoffmeister *et al.*, 2002a, 2002b; Chaffai *et al.*, 2002; Lee *et al.*, 2003a, 2003b; Laugier, 2004; Hakulinen *et al.*, 2005; Yamoto *et al.*, 2006). A landmark prospective clinical study of 5662 women showed that a linear combination of SOS and broadband ultrasound attenuation (BUA) predicts hip fracture risk in elderly women as well as dual energy x-ray absorptiometry (Hans *et al.*, 1996). Other prospective (Huopio *et al.*, 2004; Krieg *et al.*,

2006) and retrospective (Schott *et al.*, 1995; Turner *et al.*, 1995; Mautalen *et al.*, 1995, Thompson *et al.*, 1998; Krieg *et al.*, 2003; Glüer *et al.*, 2004; Maggi *et al.*, 2006) clinical studies have further established the utility of SOS for fracture risk prediction.

In laboratories and in commercial bone sonometers, SOS is usually measured in through-transmission. The ultrasound pulse transit time through the bone is compared with the transit time through a water path. SOS in bone is then computed from SOS in water, bone thickness, and transit-time differential. In order to measure transit time from digitized radio-frequency waveforms, a marker on the waveforms such as a zero-crossing is usually designated. Unfortunately, frequency-dependent attenuation and dispersion can distort waveforms, shift locations of zero-crossings, and produce variations in SOS measurements. See Figure 1. This is particularly troublesome for highly attenuating media such as bone.

Ambiguities in time-domain SOS measurements in cancellous bone were first reported by Laugier *et al.* (1993) and subsequently by Strelitzki and Evans (1996a), Nicholson *et al.* (1996) and Wear (2000a). Laugier *et al.* showed that SOS measurements in cancellous bone are highest for markers near the leading edge of the pulse waveform and lowest for markers near the trailing edge. As previously reported (Wear, 2000a) and also shown in Table I, there is a considerable range of choices for markers. Therefore, different investigators using different measurement systems and different analysis algorithms obtain disparate values for SOS, often precluding meaningful comparison and/or pooling of measurements obtained from different studies. This problem may contribute to the substantial disparity in SOS measurements from different commercial bone sonometers reported by Njeh *et al.* (2000). See Figure 2. Glüer (2007) recently emphasized that improvement in standardization methods will be required before quantitative ultrasound can play a major role in clinical practice.

Velocity measurement methods that do not rely on designated markers may be more resistant to frequency-dependent-attenuation-induced artifacts. One method estimates relative time delay from the cross correlation of the two waveforms. Unfortunately, this method becomes less robust when signals are severely distorted. In bone, substantial distortion arises from frequency-dependent attenuation, dispersion, multiple scattering, and phase cancellation. Another method utilizes phase velocity, which is measured in the frequency domain, rather than a time-domain SOS measure. Although these alternatives may have some advantages, the ultrasonic bone characterization literature is dominated by the marker-time-shift methodology discussed above (see Table I). Therefore, it is important to explore sources of variability inherent in these methods so that they may be taken into account when interpreting and comparing existing results. Moreover, although companies generally do not publish their SOS-measurement algorithms in the public domain, it is likely that many commercial systems utilize marker-time-shift SOS measurements due to their prevalence in the literature. (Note that a senior author for two of the references in Table I was the founder of Lunar—now GE Lunar—Corporation, a major manufacturer of clinical bone sonometers.) Therefore, these same sources of variability are likely to affect commercial bone sonometer measurements.

A mathematical model was previously developed to predict variations in SOS estimates for Gaussian pulses propagating through media with weak dispersion and attenuation that varies linearly with frequency (Wear, 2000a; Wear, 2001). The model was validated with measurements on 24 human calcaneus samples *in vitro*. It was shown that in human calcaneus *in vitro* the effects of attenuation are far greater than the effects of dispersion. Haïat *et al.* (2006) used an approach based on this model to investigate SOS measurements in 38 human femur samples *in vitro*. Rather than using a fixed value for dispersion, however, they compensated SOS measurements based on individual dispersion measurements. They found this approach to be very accurate in numerically predicting disparity between a zero-crossing-based SOS estimate and group velocity. Their analysis was very thorough in delineating the effects of dispersion and attenuation on SOS estimates in femur.

Although the numerical approach accurately predicts system-related and algorithm-related variations in SOS measurements, it requires substantial effort to implement and is unlikely to be widely-adopted by the research community or by industry. In order to make this problem more tractable, a simpler model, which accounts for frequency-dependent attenuation but not dispersion, is derived below. The analysis produces an analytic formula that is easy to use for the adjustment of SOS measurements performed with different measurement systems and different marker locations. The formula provides insight into the effects of system parameters (center frequency and bandwidth), algorithm parameters (marker location) and bone properties (attenuation coefficient and thickness) on time-domain SOS estimates. The formula may be used to retroactively compensate existing data. The model is validated in a bone-mimicking phantom and in 30 human calcaneus samples *in vitro*.

Theory

SOS is usually measured in through transmission. Two transducers, one transmitter and one receiver, are arranged in a “pitch-catch” orientation. First, a calibration measurement is performed by propagating a pulse from the transmitter to the receiver through a water path. Then a sample (e.g. bone) is placed between the two transducers, and a second measurement is performed. SOS may then be computed from

$$SOS = \frac{c_w}{1 + \frac{c_w \Delta t}{d}} \quad (1)$$

where c_w is the acoustic velocity in water, t is the difference in arrival times of the two pulses, and d is the thickness of the sample. Since the pulse has finite duration, a marker (e.g. the maximum or a zero crossing) is designated for the measurements of arrival times. (Of course, for the sake of consistency, the same marker must be chosen for both calibration and sample measurements.) As illustrated in Figure 1, however, frequency-dependent attenuation (which is a low-pass filter) stretches the attenuated signal in time and causes t to vary with marker designation.

In this section, a formula for the disparity in SOS measurement due to a disparity in marker designation is derived. Suppose that two markers, n and m , yield t values t_n and t_m , then the resulting disparity in SOS estimates is

$$\Delta SOS_{n,m} = \frac{c_w}{1 + \frac{c_w \Delta t_n}{d}} - \frac{c_w}{1 + \frac{c_w \Delta t_m}{d}} = \frac{c_w^2}{d} \frac{(\Delta t_m - \Delta t_n)}{\left(1 + \frac{c_w \Delta t_m}{d}\right) \left(1 + \frac{c_w \Delta t_n}{d}\right)} \quad (2)$$

In order to derive expressions for t_n and t_m for various marker designations, a model for time-domain signals undergoing frequency-dependent attenuation is taken from a previous paper (Wear, 2000a). Briefly, the water-path calibration signal, $x(t)$, is assumed to be a Gaussian modulated sinusoid, with analytic signal representation given by

$$x(t) = A e^{-t^2/2\sigma_0^2} e^{i2\pi f_0 t} \quad (3)$$

where A is the pulse magnitude, σ_0 is a measure of the pulse duration, f_0 is the center frequency, and t is time. (Throughout this section, a subscript of 0 will be used for parameters in the calibration measurement while a subscript of 1 will be used for parameters in the sample—e.g. bone—measurement.) The Fourier transform of $x(t)$ is

$$X(f) = A \sigma_0 \sqrt{2\pi} e^{-(f-f_0)^2/2\sigma_f^2} \quad (4)$$

where f is frequency and $\sigma_f = 1/(2\pi\sigma_0)$ is a measure of the bandwidth. A medium with attenuation that varies linearly with frequency can be modeled with the following transfer function,

$$H(f) = e^{-\beta f d} e^{-i2\pi f s} \quad (5)$$

where βf is the attenuation coefficient, d is the thickness of the sample, and s is the time delay (relative to a water reference signal) given by

$$s = d \left[\frac{1}{c_b} - \frac{1}{c_w} \right] \quad (6)$$

where c_b is the phase velocity in the linearly-attenuating medium. (Note that $s < 0$ when $c_b > c_w$.) It can be shown that the attenuated signal, $y(t)$, takes the form (Wear, 2000a)

$$y(t) = B e^{-(t-s)^2/2\sigma_1^2} e^{i2\pi f_1(t-s)} \quad (7)$$

where B is the pulse magnitude, and σ_1 is a measure of the pulse duration. The down-shifted center frequency, f_1 , of the attenuated wave is given by (Narayana and Ophir, 1983; Wear, 2000a)

$$f_1 = f_0 - \sigma_f^2 \beta d \quad (8)$$

Locations of zero crossings are determined by the complex exponential factors in Equations 3 and 7. The locations of zero-crossing markers for the symmetric pulses shown in Figure 1 are given in Table II.

Suppose that a marker on the calibration signal, $x(t)$, is chosen at $t = t_{n0}$. Then, by comparing the complex exponentials in Equations 3 and 7, it can be seen that the corresponding marker on the attenuated waveform, t_{n1} , will satisfy $f_0 t_{n0} = f_1(t_{n1} - s)$. Therefore, $t_{n1} = (f_0/f_1)t_{n0} + s$. The transit time differential is then

$$\Delta t_n = t_{n1} - t_{n0} = \left(\frac{f_0}{f_1} - 1 \right) t_{n0} + s = a t_{n0} + s \quad (9)$$

where (using Equation 8)

$$a \equiv \frac{f_0}{f_1} - 1 = \frac{f_0}{f_0 - \sigma_f^2 \beta d} - 1 = \frac{\sigma_f^2 \beta d}{f_0 - \sigma_f^2 \beta d} \quad (10)$$

Equation (2) compares the SOS estimate based on marker n located at t_{n0} with the SOS estimate based on marker m located at t_{m0} . Suppose that the second marker (m) is chosen to be the envelope maximum, so that the second SOS estimate corresponds to group velocity. If the reference pulse is assumed to be centered at the origin, then $t_{m0} = 0$, $t_{m1} = s$, and $t_m = s$. The difference of transit-time differentials for two markers required in the numerator of Equation 2 is then (from Equation 9)

$$\Delta t_m - \Delta t_n = -a t_{n0} = -a \frac{\tau}{f_0} \quad (11)$$

where τ is the interval between calibration marker n and the envelope maximum, measured in units of the calibration waveform period, $T_0 = 1/f_0$, so that $\tau \equiv t_{n0}/T_0 = f_0 t_{n0}$. For example, the central zero crossings on the symmetric calibration waveform in Figure 1 occur at $\tau = \dots -5/4, -3/4, -1/4, 1/4, 3/4, 5/4 \dots$

Equation 11 gives the numerator for the right hand factor in Equation 2. Now the denominator for the right hand factor in Equation 2 must be obtained. Let c_g denote group velocity. Note from Equation (1) that

$$c_g = \frac{c_w}{1 + \frac{c_w s}{d}} \quad (12)$$

Now the denominator from Equation 2 may be simplified as follows.

$$\left(1 + \frac{c_w s}{d} \right) \left[1 + \frac{c_w}{d} \left(\frac{a\tau}{f_0} + s \right) \right] = \frac{c_w}{c_g} \left[\frac{c_w}{c_g} + \frac{c_w a\tau}{d f_0} \right] = \frac{c_w^2}{c_g^2} + \frac{c_w^2 a\tau}{c_g d f_0} \quad (13)$$

Combining Equations 2, 11 and 13 yields

$$SOS_n - c_g = -c_g \frac{a\tau}{\frac{f_0 d}{c_g} + a\tau} \quad (14)$$

In the ultrasonic characterization of bone, the first term in the denominator of Equation (14) will often dominate the second term. For example, using typical values ($f_0 = 500$ kHz, $\sigma_f = 100$ kHz, normalized broadband ultrasound attenuation or $nBUA = 30$ dB/cmMHz, $\beta = nBUA / 8.68 = 3.5$ 1/cmMHz, $d = 2$ cm, $c_g = 1500$ m/s $\rightarrow a = 0.16$, and $\tau = -1.25$), the two terms become 6.67 and -0.20 respectively. Neglecting the second term in the denominator, Equation (14) simplifies to

$$SOS_n - c_g \approx -\frac{c_g^2 a \tau}{f_0 d} = -\frac{\tau c_g^2 \sigma_f^2 \beta}{f_0^2} \frac{1}{1 - (\sigma_f^2 \beta d / f_0)} \quad (15)$$

Equation (15) shows that the magnitude of the deviation of the SOS estimate from group velocity has a strong dependence on the fractional bandwidth (σ_f / f_0). The disparity of SOS estimates derived from two arbitrary markers, n and m , separated by τ , is given by

$$\Delta SOS_{n,m} \approx -\frac{\Delta \tau c_g^2 \sigma_f^2 \beta}{f_0^2} \frac{1}{1 - (\sigma_f^2 \beta d / f_0)} \quad (16)$$

Methods

A. Bone samples and phantom

30 human calcaneus samples (both genders, ages unknown) were defatted using a trichloroethylene solution. Defatting was presumed not to significantly affect measurements since SOS of defatted trabecular bone has been measured to be only slightly different from that of bone with marrow left intact (Njeh and Langton, 1998; Alves *et al.*, 1996a). The cortical lateral layers were sliced off leaving two parallel surfaces with direct access to trabecular bone. Since cortical layers are so thin (a few mm), their removal does not alter SOS measurements very much; an experimental investigation of SOS from 20 human calcanea, both before and after cortical plate removal, showed that calcaneal SOS is determined mainly by the cancellous bone component (Njeh and Langton, 1997a). The thicknesses of the samples varied from 12 to 21 mm. In order to remove air bubbles, the samples were vacuum degassed underwater in a desiccator. After vacuum, samples were allowed to thermally equilibrate to room temperature prior to ultrasonic interrogation. Ultrasonic measurements were performed in distilled water at room temperature. The temperature was not actively controlled but was measured for each experiment and ranged between 19°C and 22°C. The relative orientation between the ultrasound beam and the calcanea was the same as with *in vivo* measurements performed with commercial bone sonometers, in which sound propagates in the mediolateral (or lateromedial) direction.

A quantitative ultrasound phantom (Model 063, CIRS inc., Norfolk, VA) was also interrogated. The phantom was composed of proprietary urethane and had a thickness of 36

mm (http://cirsinc.com/063_ultra.html). The attenuation coefficient slope (nBUA) was measured to be 15.0 dB/cmMHz (at 19.3 degrees Celsius). (The model 063 contains two phantoms labeled “normal” and “osteoporotic.” The “osteoporotic” phantom was measured here.)

B. Ultrasonic measurements

Bone samples and the phantom were interrogated in through-transmission in a water tank using a Panametrics (Waltham, MA) 5800 pulser/receiver with pairs of coaxially-aligned Panametrics transducers. See Table III. Received signals were digitized (8 bits; 10 MHz for bone data, 25 MHz for phantom data) using a LeCroy (Chestnut Ridge, NY) 9310C Dual 400 MHz oscilloscope and stored on computer (via GPIB) for off-line analysis.

The temperature-dependent speed of sound in distilled water, c_w , was used as the reference speed and is given by (Kaye and Laby, 1973)

$$c_w = 1402.9 + 4.835T - 0.047016 T^2 + 0.00012725 T^3 \quad (17)$$

where T is the temperature in degrees Celsius. Analysis software was written in MATLAB (Natick, MA). Each arrival time was computed as follows. The mean (dc) value of each received signal was subtracted. The signal was filtered with a frequency domain Gaussian filter with center frequency equal to the transducer nominal center frequency and standard deviation equal to 125 kHz (500 kHz data) or 200 kHz (1 MHz data). The envelope was computed using the Hilbert transform. The three zero crossings immediately before (L1, L2, and L3 in Figure 1) and after (T1, T2, and T3) the radio-frequency maximum were measured using linear interpolation between points at which a change in sign occurred.

“Uncompensated” SOS values were computed directly using equation 1. “Compensated” SOS values were computed by subtracting the predicted SOS difference from group velocity—computed using either Equation (14) or (15)—from the uncompensated SOS values. Spectral parameters (f_0 and σ_f), which are required for Equations (14) and (15), were estimated from Gaussian fits to measured water-path spectra. Attenuation coefficients, which are also required in Equations (14) and (15), were computed from linear least squares fits to log spectral differences vs. frequency over the range from 300 to 600 kHz (Narayana and Ophir, 1983; Wear, 2000a).

Generally speaking, this substitution technique can exhibit appreciable error if the speed of sound differs substantially between the sample and the reference (Kaufman *et al.*, 1995). However, one study indicates that this diffraction-related error is negligible in calcaneus (Droin *et al.*, 1998). Apparently, the speed of sound in calcaneus, approximately 1475 – 1650 m/s, (Droin *et al.*, 1998) is sufficiently close to that of distilled water at room temperature, 1487 m/s (from Equation 17) that diffraction-related errors may be ignored.

The effect of system spectral properties (f_0 and σ_f) was investigated by simulating four different systems obtained by applying four different Gaussian filters (instead of the filters described above) to the radio-frequency data acquired after transmission through the CIRS bone-mimicking phantom (see Table IV). SOS was measured using three zero crossings

from the leading half of the pulse (L1, L2, and L3). Uncompensated measurements were compared with measurements compensated using Equation 14.

Results

A. Simulation

Estimates for SOS in equations (14) and (15) were compared to estimates generated using a previously-published numerical method (Wear, 2000a) in which 1) a simulated Gaussian pulse is generated, 2) an FFT is applied, 3) the dispersive form of the transfer function in Equation 5 is applied (See Wear, 2000a, Equations 3, 4 and 11), 4) an inverse FFT is applied, and 5) zero crossing locations are located on the resulting time-domain waveform. For this simulation, the following parameter values were assumed: $f_0 = 500$ kHz, $\sigma_f = 100$ kHz, $d = 2$ cm, and $c_g = 1550$ m/s. Figure 3 shows theoretical (Equation 14) and numerical results for disparity between SOS and group velocity evaluated at leading edge zero crossings L1, L2, and L3 for the non-dispersive case. There is excellent agreement between theoretical and numerical results. Figure 4 shows theoretical results for disparity between SOS and group velocity using Equation (14) and its approximate form, Equation (15). Again, excellent agreement is found.

Figure 5 shows numerical results for the effect of dispersion on the disparity between SOS and group velocity evaluated at leading edge zero crossing L3. Mean *in vitro* calcaneal dispersion rates from four published studies (see Table V) range from -15 to -40 m/sMHz, with an average value of -26.25 m/sMHz. According to Figure 5, a typical dispersion rate of -25 m/sMHz has a small effect on the disparity between SOS and group velocity.

B. Experiments

Figure 6 shows the disparity between SOS and group velocity at 500 kHz for 30 bone samples *in vitro* evaluated at zero crossings L3, L2, L1, T1, T2, and T3. The steady decline in uncompensated SOS as marker is moved from the leading edge toward the trailing edge, originally reported by Laugier (1993), is evident. The compensation formula (Equation 14) effectively suppresses the dependence of SOS on marker location.

Figure 7 shows the disparity between SOS and group velocity at 1 MHz for 24 bone samples *in vitro* evaluated at zero crossings L3, L2, L1, T1, T2, and T3. Again, the compensation formula (Equation 14) effectively suppresses the dependence of SOS on marker location.

Figure 8 shows filtered power spectra simulating four different data acquisition systems. Figure 9 shows uncompensated estimates of SOS from the CIRS bone-mimicking phantom evaluated at zero crossings L3, L2, L1 and at the envelope maximum (c_g). Figure 9 shows that system-related variations in SOS decrease as the marker moves toward the pulse center. Relatively subtle changes in system fractional bandwidth can lead to considerable variations in SOS estimate, particularly for markers near the leading edge. Figure 10 shows compensated estimates of SOS from the CIRS bone-mimicking phantom evaluated at zero crossings L3, L2, L1 and at the envelope maximum (c_g). The compensation formula (Equation 14) effectively suppresses the dependence of SOS on marker location and system center frequency and bandwidth.

Discussion

As Njeh (2000) recently reported, SOS measurements vary widely among commercial systems (see Figure 2). Glüer (2007) recently emphasized that improvement in standardization methods will be required before quantitative ultrasound can play a major role in clinical practice. This paper presents a framework for understanding the effects of system parameters (center frequency and bandwidth), algorithm parameters (marker location) and bone properties (attenuation coefficient and thickness) on time-domain SOS estimates. The framework was validated with measurements in a bone-mimicking phantom and in 30 human calcaneus samples *in vitro*. The success of this model suggests that accurate predictions of variations in SOS estimates in human calcaneus *in vitro* may be made even when the effects of dispersion are ignored. Other potential sources of disparity in the SOS measurement—including variations in region of interest location, variations in temperature, assumptions regarding heel thickness—are not considered here.

The variation of SOS with transit-time marker is significant. For example, at 500 kHz, average SOS changes by about 8 m/s when transit-time marker shifts from L3 to L2 (see Figure 6). This is a substantial amount compared with average SOS differences between patients with hip fractures and age-matched controls, which have been reported to be 25 m/s (Schott *et al.*, 1995), 28 m/s (Mautalen *et al.*, 1995), 13.5 m/s (Hans *et al.*, 1996), 20 m/s (Njeh *et al.*, 2000—see Figure 2), and 20 m/s (Krieg *et al.*, 2006). The variation of SOS with transit-time marker is also substantial when compared to many of the inter-system differences reported by Njeh *et al.* (2000) which are often on the order of 20 – 40 m/s (see Figure 2).

Equation (16) provides a means for comparing SOS estimates, SOS_n and SOS_m , based on different marker times separated by τ . In the case of high $a\tau$, it may be necessary to instead use Equation (14) twice (first to compute the difference between SOS_n and c_g , and again to compute the difference between SOS_m and c_g) and then to take the difference between the two differences to yield $SOS_n - SOS_m$. Therefore, data acquired using different systems and computed using different marker times can be compensated to facilitate comparison or pooling provided that the following variables are known: f_0 , σ_f , β , d , and c_g . The first two variables may be estimated by performing spectral analysis on a water-path measurement. Attenuation coefficient slope β may be computed from BUA, which is measured by most calcaneal systems, and d , which may be measured *in vitro* or even *in vivo* (Chen *et al.*, 2005; Yi *et al.*, 2007) or if necessary set to an average value (e.g. Nicholson *et al.*, 1997, measured an average value of 25 mm from 28 female calcanea). Finally, although c_g may not be known, a typical value may be assumed. For example, c_g in human calcaneus *in vitro* has been reported to range from 1475 – 1575 m/s (Wear, 2000b). So a typical value of 1525 m/s may be assumed, producing an error of no more than seven percent in equations (14) – (16).

In order to circumvent problems associated with time-domain SOS measures, some authors have suggested the use of phase velocity, which is measured in the frequency domain, to characterize bone (Alves *et al.*, 1996a; Nicholson *et al.*, 1996; Strelitzki and Evans, 1996b; Droin *et al.*, 1998). The framework presented in this paper provides a method for retroactively estimating phase velocity from time-domain SOS measurements. First,

Equation 14 may be used to estimate group velocity, c_g . Then, the following relation may be used to estimate phase velocity, c_{pc} , at the center frequency, f_c (Morse and Ingard, 1986, and Duck, 1990)

$$c_g = \frac{c_{pc}}{1 - \frac{f_c}{c_{pc}} \left(\frac{\partial c_{pc}}{\partial f} \right)_{f=f_c}}$$

The quantity in parentheses is the dispersion rate. If independent dispersion measurements are not available, a typical value, such as those listed in Table V may be assumed.

The framework presented here can provide some insight into why many investigators choose markers near the leading edge of the pulse waveform. Attenuation and sound speed tend to increase with density. From Equation 15, it can be seen that SOS estimates based on markers near the leading edge are boosted by higher attenuation values (recall that τ is negative on the leading half of the pulse). So, for example, in order to increase the sensitivity of the SOS estimate to density, it might be tempting to use a marker near the leading edge. Indeed, Haïat *et al.* (2006) found that SOS measurements based on the first zero crossing have a higher correlation with BMD in femur *in vitro* than group velocity (see Haïat *et al.*, 2006, Table II). Therefore, a marker near the leading edge might be preferable when a single parameter (SOS) is used to assess the bone, as is the case with current cortical bone systems and may be the case with future femur systems. Most calcaneal systems, however, use a linear combination of BUA and SOS to assess the bone. For these systems, the quantitative diagnostic classifier should be able to properly account for attenuation effects directly by optimally adjusting the weighting coefficient for BUA, without the need to enhance SOS measurements by an amount related to BUA. Indeed, Haïat *et al.* (2006) also found that SOS measurements based on the first zero crossing performed comparably to group velocity when either was used *in combination with BUA* in a multiple regression model (again see Haïat *et al.*, 2006, Table II).

As elegantly explored by Haïat *et al.* (2006), zero-crossing-based measures of SOS are prone to discontinuous jumps as BUA or dispersion varies. These jumps are due to changes in the pulse shape that alter reference points along the pulse in such a way to shift the marker locations by one or more zero-crossing intervals. Since group velocity is derived from the envelope, it is more immune to these effects. Haïat *et al.* rightly point out, however, that markers near the leading edge are less sensitive to multi-path interference. In the femur (the bone studied by Haïat *et al.*), which has a more complicated shape than the calcaneus, these multi-path interference effects may be sufficiently problematic to justify a preference for a leading-edge zero-crossing marker.

Although calcaneal SOS is an effective predictor of fracture risk, its clinical utility is compromised by the high inter-system variability of the measurement. This paper presents a framework for standardization of SOS measurements. System-related variations in SOS decrease as the pulse-arrival-time marker moves toward the pulse center. Therefore, compared with other time-domain measures of calcaneal SOS, group velocity exhibits the

minimum system dependence. When SOS is used in combination with BUA in a linear classifier, the choice of group velocity instead of a zero-crossing-based value should not compromise diagnostic performance.

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References

- Alves JM, Xu W, Lin D, Siffert RS, Ryaby JT, and Kaufmann JJ, (1996a), Ultrasonic assessment of human and bovine cancellous bone: a comparison study, *IEEE Trans. Biomed. Eng* 43, 249–258. [PubMed: 8682537]
- Alves JM, Ryaby JT, Kaufman JJ, Magee FP, and Siffert RS, (1996b), Influence of marrow on ultrasonic velocity and attenuation in bovine trabecular bone, *Calcif. Tissue Int*, 58, 362–367. [PubMed: 8661972]
- Bauer DC, Gluer CC, Cauley JA, Vogt TM, Ensrud KE, Genant HK, and Black DM, (1997) “Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women,” *Arch. Intern. Med.* 157, 629–634. [PubMed: 9080917]
- Bouxsein ML, and Radloff SE. (1997), “Quantitative ultrasound of the calcaneus reflects the mechanical properties of calcaneal trabecular bone,” *J. Bone Miner. Res* 12, pp. 839–846. [PubMed: 9144351]
- Chaffai S, Peyrin F, Nuzzo S Porcher R, Berger G, and Laugier P, (2002), “Ultrasonic characterization of human cancellous bone using transmission and backscatter measurements: relationships to density and microstructure,” *Bone*, 30, 229–237. [PubMed: 11792590]
- Chen P, Chen T, Lu M, and Yao W, (2005), The measurements of ultrasound parameters on calcaneus by two-sided interrogation techniques, *Meas. Sci. & Tech*, 16, 1349–1354.
- Droin P, Berger G and Laugier P, (1998), “Velocity dispersion of acoustic waves in cancellous bone.” *IEEE Trans. Ultrason. Ferro. Freq. Cont* 45, 581–592.
- Duck FA, *Physical properties of tissue*. (1990), University Press, Cambridge, U. K.
- Glüer CC, Eastell R, Reid DM, Felsenbert D, Roux C, Barkmann R, Timm W, Blenk T, Armbrrecht G, Stewart A, Clowes J, Thomasius FE, and Kolta S, (2004), “Association of five quantitative ultrasound devices and bone densitometry with osteoporotic vertebral fractures in a population-based sample: the OPUS study,” *J. Bone Miner. Res*, 19, 782–793. [PubMed: 15068502]
- Glüer CC, (2007), Quantitative ultrasound—it is time to focus research efforts, *Bone*, 40, 9–13. [PubMed: 16949359]
- Haïat G, Padilla F, Barkmann R, Kolta S, Latremouille C, Glüer CC, and Laugier P (2005), In vitro speed of sound measurement at intact human femur specimens, *Ultrasound in Med. & Biol.* 31, 987–996. [PubMed: 15972205]
- Haïat G, Padilla F, Cleveland RO, and Laugier P (2006), Effects of frequency-dependent attenuation and velocity dispersion on in vitro ultrasound velocity measurements in intact human femur specimens,” *IEEE Trans Ultrason. Ferro. Freq. Cont*, 53, 39–51.
- Hakulinen MA, Day JS, Toyra J, Timonen M, Kroger H, Weinans H, Kiviranta I, and Jurvelin JS, (2005), Prediction of density and mechanical properties of human trabecular bone in vitro by using ultrasound transmission and backscattering measurements at 0.2 – 6.7 MHz frequency range, *Phys. Med. Biol* 50, 1629–1642. [PubMed: 15815086]
- Hans D, Dargent-Molina P, Schott AM, Sebert JL, Cormier C, Kotzki PO, Delmas PD, Pouilles JM, Breart G, and Meunier PJ (1996), “Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study,” *Lancet*, 348, 511–514. [PubMed: 8757153]

- Hans D, Wu C, Njeh CF, Zhao S, Augat P, Newitt D, Link T, Lu Y, Majumdar S, and Genant HK (1999), "Ultrasound velocity of cancellous cubes reflects mainly bone density and elasticity," *Calcif. Tissue Intl.* 64, 18–23.
- Hoffmeister BK, Whitten SA, and Rho JY, (2000), "Low-megahertz ultrasonic properties of bovine cancellous bone," *Bone*, 26, 635–642. [PubMed: 10831936]
- Hoffmeister BK, Whitten SA, Kaste SC and Rho JY, (2002a), "Effect of collagen and mineral content on the high-frequency ultrasonic properties of human cancellous bone," *Osteo. Int'l*, 13, 26–32.
- Hoffmeister BK, Auwarter JA, and Rho JY, (2002b), "Effect of marrow on the high frequency ultrasonic properties of cancellous bone," *Phys. Med. Biol.* 47, 3419–3427. [PubMed: 12375829]
- Huopio J, Kroger H, Honkanen R, Jurvelin J, Saarikoski S, and Alhava E, (2004), "Calcaneal ultrasound predicts early postmenopausal fractures as well as axial BMD. A prospective study of 422 women," *Osteo. Int.* 15, 190–195.
- Kaufman JJ, Xu W, Chiabrera AE, and Siffert RS, (1995), "Diffraction effects in insertion mode estimation of ultrasonic group velocity," *IEEE Trans. Ultrason. Ferroelectr. Freq. Cont.* 42, 232–242.
- Kaye GWC, and Laby TH (1973), *Table of Physical and Chemical Constants*. London, UK: Longman.
- Krieg MA, Cornuz J, Ruffieux C, et al., (2003), "Comparison of three bone ultrasound for the discrimination of subjects with and without osteoporotic fractures among 7562 elderly women," *J. Bone & Mineral Res.* 18, 1261–1266.
- Krieg MA, Cornuz J, Ruffieux C, et al., (2006) "Prediction of hip fracture risk by quantitative ultrasound in more than 7000 Swiss women > 70 years of age: comparison of three technologically different bone ultrasound devices in the SEMOF study," *J. Bone & Mineral Res.* 21, 1457–1463.
- Langton CM, Njeh CF, Hodgkinson R, and Currey JD, (1996), "Prediction of mechanical properties of the human calcaneus by broadband ultrasonic attenuation," *Bone*, 18, 495–503. [PubMed: 8805988]
- Laugier P, Giat P, Droin P, Saied A, and Berger G (1993), *Ultrasound images of the os calcis: a new method of assessment of bone status*. *Proc. 1993 IEEE Ultrasonics Symp.* vol.2, 989–92.
- Laugier P, Droin P, Laval-Jeantet AM, and Berger G (1997), "In vitro assessment of the relationship between acoustic properties and bone mass density of the calcaneus by comparison of ultrasound parametric imaging and quantitative computed tomography," *Bone*. 20, 157–165. [PubMed: 9028541]
- Laugier P, "An overview of bone sonometry," (2004), *International Congress Series*, 1272, 23–32.
- Lee KL, Roh H, and Yoon SW, (2003a), *Correlations between acoustic properties and bone density in bovine cancellous bone from 0.5 to 2 MHz*, *J. Acoust. Soc. Am.* 113, 2933–2938. [PubMed: 12765411]
- Lee KI, Roh H, and Yoon SW (2003b), "Acoustic wave propagation in bovine cancellous bone: Application of the modified Biot-Attenborough model," *J. Acoust. Soc. Am.* 114, 2284–2293. [PubMed: 14587625]
- Maggi S, Noale M, Gianinini S, et al. (2006), "Quantitative heel ultrasound in a population-based study in Italy and its relationship with fracture history: the ESOPO study," *Osteo. Int.* 17, 237–244.
- Mautalen C, Vega E, Gonzalez D, Carrilero P, Otano A, and Silberman F, "Ultrasound and dual x-ray absorptiometry densitometry in women with hip fracture," (1995) *Calcif. Tissue Int.* 57, 165–168. [PubMed: 8574930]
- Morse PM, and Ingard KU, (1986), *Theoretical Acoustics*. Princeton University Press, Princeton, NJ, chapter 9.
- Narayana PA, and Ophir J, (1983), "A closed form method for the measurement of attenuation in nonlinearly dispersive media," *Ultrason. Imag.* 5, 17–21.
- Nicholson PHF, Lowet CG, Langton CM, Dequeker J, and Van der Perre G, (1996), "Comparison of time-domain and frequency-domain approaches to ultrasonic velocity measurements in cancellous bone," *Phys. Med. Biol.* 41, 2421–2435. [PubMed: 8938036]
- Nicholson PHF, Lowet G, Cheng XG, Boonen S, Van der Perre G, and Dequeker J (1997), "Assessment of the strength of the proximal femur in vitro: relationship with ultrasonic measurements of the calcaneus," *Bone*, 20, 219–224. [PubMed: 9071472]

- Nicholson PHF, Muller R, Lowet G, Cheng XG, Hildebrand T, Ruegsegger P, Van Der Perre G, Dequeker J, and Boonen S, (1998), "Do quantitative ultrasound measurements reflect structure independently of density in human vertebral cancellous bone?," *Bone*, 23, 425–431. [PubMed: 9823448]
- Njeh CF, Hodgkinson R, Currey JD, and Langton CM, (1996), Orthogonal relationships between ultrasonic velocity and material properties of bovine cancellous bone, *Med. Eng. Phys.*, 18, 373–381. [PubMed: 8818135]
- Njeh CF, and Langton CM, (1997a), The effect of cortical endplates on ultrasound velocity through the calcaneus: an in vitro study, *Brit. J. Radiol.*, 70, 504–510. [PubMed: 9227233]
- Njeh CF, Kuo CW, Langton CM, Atrah HI, and Boivin CM, (1997b), Prediction of human femoral bone strength using ultrasound velocity and BMD: an in vitro study. *Osteo. Int'l.*, 7, 471–477.
- Njeh CF, Hans D, Li J, Fan B, Fuerst T, He YQ, Tsuda-Futami E, Lu Y, Wu CY, and Genant HK, (2000), Comparison of six calcaneal quantitative ultrasound devices: precision and hip fracture discrimination, *Osteo. Int.*, 11, 1051–1062.
- Rossman P, Zagzebski J, Mesina C, Sorenson J and Mazess R, (1989), Comparison of Speed of Sound and Ultrasound Attenuation in the Os Calcis to Bone Density of the Radius, Femur and Lumbar Spine, *Clin. Phys. Physiol. Meas.*, 10, 353–360, 1989. [PubMed: 2698780]
- Schott M, Weill-Engerer S, Hans D, Duboeuf F, Delmas PD, and Meunier PJ, (1995), "Ultrasound discriminates patients with hip fracture equally well as dual energy X-ray absorptiometry and independently of bone mineral density," *J. Bone Min. Res.*, 10, 243–249.
- Strelitzki R, Clarke AJ, and Evans JA, (1996a), The measurement of the velocity of ultrasound in fixed trabecular bone using broadband pulses and single-frequency tone bursts, *Phys. Med. Biol.*, 41, 743–753. [PubMed: 8730667]
- Strelitzki R, and Evans JA, (1996b), On the measurement of the velocity of ultrasound in the os calcis using short pulses, *Eur. J. Ultrasound*, 4, pp. 205–213.
- Strelitzki R, Evans JA, and Clarke AJ, (1997), "The influence of porosity and pore size on the ultrasonic properties of bone investigated using a phantom material," *Osteo. Int.*, 7, 370–375.
- Tavakoli MB and Evans JA (1991) "Dependence of the velocity and attenuation of ultrasound in bone on the mineral content," *Phys. Med. Biol.*, 36, 1529–1537. [PubMed: 1754623]
- Thompson P, Taylor J, Fisher A, and Oliver R, (1998), "Quantitative heel ultrasound in 3180 women between 45 and 75 years of age: compliance, normal ranges and relationship to fracture history," *Osteo. Int'l.*, 8, 211–214.
- Trebacz H, and Natali A (1999), Ultrasound velocity and attenuation in cancellous bone samples from lumbar vertebra and calcaneus, *Osteo. Int'l.*, 9, 99–105.
- Turner H, Peacock M, Timmerman L, Neal JM, and Johnston CC Jr., (1995), "Calcaneal ultrasonic measurements discriminate hip fracture independently of bone mass," *Osteo. International*, 5, 130–135.
- Wear KA, (2000a), "The effects of frequency-dependent attenuation and dispersion on sound speed measurements: applications in human trabecular bone", *IEEE Trans Ultrason. Ferro. Freq. Cont.*, 47, 265–273.
- Wear KA, (2000b), Measurements of phase velocity and group velocity in human calcaneus, *Ultrasound Med. Biol.*, 26, 641–646. [PubMed: 10856627]
- Wear KA, (2001), A numerical method to predict the effects of frequency-dependent attenuation and dispersion on speed of sound estimates in cancellous bone," *J. Acoust. Soc. Am.*, 109, 1213–1218. [PubMed: 11303934]
- Yamoto Y, Matsukawa M, Otani T, Yamazaki K, and Nagano A, (2006), "Distribution of longitudinal wave properties in bovine cortical bone in vitro," *Ultrasonics*, 44, e233–e237. [PubMed: 16860358]
- Yi Xia, Lin Wei, and Qin Yi-Xian, (2007), Bone surface topology mapping and its role in trabecular bone quality assessment using scanning confocal ultrasound, *Osteo. Int.*, in press.
- Zagzebski JA, Rossman PJ, Mesina C, Mazess RB, and Madsen EL, (1991), Ultrasound transmission measurements through the os calcis, *Calcif. Tissue Int.*, 49, 107–111. [PubMed: 1913288]

Figure 1.

The effect of frequency-dependent attenuation on transit-time differential, Δt . Markers are labeled with an L for leading half or a T for trailing half and are numbered outward from the pulse center. The variation in Δt with marker location is due to the fact that the attenuated pulse is stretched in time as a consequence of the low-pass filtering effect of frequency-dependent attenuation.

Figure 2.
SOS measurements reported by Njeh *et al.* (2000) in 35 normal post-menopausal women and 35 age-matched women with fractures using six commercial bone sonometers.

Figure 3.

Theoretical and numerical results for disparity between SOS and group velocity evaluated at leading edge zero crossings L1, L2, and L3. The range of nBUA considered here is similar to that reported from experimental investigations of human calcaneus *in vitro* (Langton *et al.*, 1996).

Figure 4.

Theoretical results for disparity between SOS and group velocity using Equation (14) and its approximate form, Equation (15).

Figure 5.

Effect of dispersion on the disparity between SOS and group velocity evaluated at leading edge zero crossing L3.

Figure 6.

The disparity between SOS and group velocity at 500 kHz for 30 bone samples *in vitro* evaluated at zero crossings L3, L2, L1, T1, T2, and T3. The compensated measurements were compensated using Equation 14.

Figure 7.

The disparity between SOS and group velocity at 1 MHz for 24 bone samples *in vitro* evaluated at zero crossings L3, L2, L1, T1, T2, and T3. The compensated measurements were compensated using Equation 14.

Figure 8.
Filtered power spectra to simulate four different data acquisition systems.

Figure 9.

Estimates of SOS (uncompensated) from the CIRS phantom evaluated at zero crossings L3, L2, L1 and at the envelope maximum (c_g). The standard deviations for all these values are less than 1.5 m/s.

Figure 10.

Estimates of SOS (compensated using Equation 14) from the CIRS phantom evaluated at zero crossings L3, L2, L1 and at the envelope maximum (c_g). The standard deviations for all these values are less than 1.5 m/s.

Table I.

A non-exhaustive listing of marker designations for SOS measurements in bone.

General Marker Type	Specific location	References
Leading edge (first detectable deviation from zero)		Njeh, <i>et al.</i> , 1996, 1997a, 1997b
Thresholding	at 3 times the noise standard deviation	Alves <i>et al.</i> , 1996a
	at 20% of amplitude of first half cycle	Hakulinen <i>et al.</i> , 2005.
Zero Crossings	first	Nicholson <i>et al.</i> , 1998; Trebacz and Natali, 1999; Lee <i>et al.</i> , 2003
	“specific”	Rossmann <i>et al.</i> , 1989.
	of first negative slope	Zagzebski <i>et al.</i> , 1991.
	first after threshold of 10%	Haïat <i>et al.</i> , 2006
	first after threshold of 15%	Haïat <i>et al.</i> , 2005
Maximum Absolute Value		Alves <i>et al.</i> , 1996b.
Maximum Envelope		Wear, 2000b

Table II.

Locations of zero-crossings for the reference and attenuated pulses shown in Figure 1. The maximum of the reference pulse is halfway between L1 and T1 at $t_0 = 0$. The period of the reference pulse is $1/f_0$. The period of the attenuated pulse is $1/f_I$.

Zero Crossing	L3	L2	L1	T1	T2	T3
Reference pulse (t_0)	$-5/4f_0$	$-3/4f_0$	$-1/4f_0$	$1/4f_0$	$3/4f_0$	$5/4f_0$
Attenuated pulse (t_I)	$-5/4f_I + s$	$-3/4f_I + s$	$-1/4f_I + s$	$1/4f_I + s$	$3/4f_I + s$	$5/4f_I + s$

Table III.

Properties of ultrasound transducers

Nominal Center Frequency (MHz)	Diameter (mm)	Focal Length (mm)
0.5	25.4	38.1
1.0	25.4	50.8

Table IV.

Four systems were simulated by filtering 500 kHz radio-frequency data with Gaussian filters with the characteristics above.

System	Filter f_0 (kHz)	Filter σ_f (kHz)	Signal f_0 (kHz)	Signal σ_f (kHz)	Fractional Bandwidth (σ_f/f_0)
#1	600	100	580	84	15%
#2	600	135	560	102	18%
#3	500	150	500	110	22%
#4	500	200	500	126	25%

Table V.

Estimates of the first derivative of phase velocity with respect to frequency, dc_p/df , in human calcaneus from Nicholson *et al.* (1996, Table 1), Strelitzki and Evans (1996, Table 2), Droin, *et al.* (1998, Table 1), and Wear (2000a, Table 1). N is the number of calcaneus samples upon which measurements were based.

Author(s)	N	Frequency Range (kHz)	dc_p/df (mean $\pm$ standard deviation) (m/s/MHz)
Nicholson <i>et al.</i>	70	200 – 800	–40
Strelitzki and Evans	10	600 – 800	–32 $\pm$ 27
Droin, Berger, and Laugier	15	200 – 600	–15 $\pm$ 13
Wear	24	200 – 600	–18 $\pm$ 15