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Solid volume fraction estimation of bone:marrow replica models using ultrasound transit time spectroscopy

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ABSTRACT

The acceptance of broadband ultrasound attenuation (BUA) for the assessment of osteoporosis suffers from a limited understanding of both ultrasound wave propagation through cancellous bone and its exact dependence upon the material and structural properties. It has recently been proposed that ultrasound wave propagation in cancellous bone may be described by a concept of parallel sonic rays; the transit time of each ray defined by the proportion of bone and marrow propagated. A Transit Time Spectrum (TTS) describes the proportion of sonic rays having a particular transit time, effectively describing the lateral inhomogeneity of transit times over the surface aperture of the receive ultrasound transducer. The aim of this study was to test the hypothesis that the solid volume fraction (SVF) of simplified bone:marrow replica models may be reliably estimated from the corresponding ultrasound transit time spectrum. Transit time spectra were derived via digital deconvolution of the experimentally measured input and output ultrasonic signals, and compared to predicted TTS based on the parallel sonic ray concept, demonstrating agreement in both position and amplitude of spectral peaks. Solid volume fraction was calculated from the TTS; agreement between true (geometric calculation) with predicted (computer simulation) and experimentally-derived values were R^2 = 99.9% and R^2 = 97.3% respectively. It is therefore envisaged that ultrasound transit time spectroscopy (UTTS) offers the potential to reliably estimate bone mineral density and hence the established *T*-score parameter for clinical osteoporosis assessment.

1. Introduction

According to Osteoporosis Australia "one in two women and one in three men over 60 years will have an osteoporotic fracture in Australia" [1] with the absolute numbers rising due to an increasing aged population. Globally, osteoporosis affects more than 200 million people and it is estimated that an osteoporotic fracture occurs every 3 s [2]. Osteoporosis is clinically defined as "a decrease in bone mass and architectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk" [3]. Clinical management of osteoporosis can be expensive as osteoporotic fractures often lead to a cascade of new fractures and additional health costs [4]; for this reason, early diagnosis and intervention are essential for successful osteoporotic fracture prevention.

A subject's skeletal status is generally determined by measuring their bone mineral density (BMD) at the hip and spine by dual energy X-ray absorptiometry (DXA). World Health Organisation (WHO) criteria for osteopenia (mild osteoporosis) and osteoporosis are defined by *T*-scores between −1 and −2.5, and below −2.5, respectively; the *T*-score for a particular subject's BMD measurement being defined as the number of BMD standard deviations below the 'young normal population' mean BMD value. DXA however has the disadvantages of being expensive, not available everywhere, time consuming and exposes the patient to ionizing radiation. An alternative diagnostic technique is quantitative ultrasound (QUS), that offers a number of measurement parameters including broadband ultrasound attenuation (BUA), speed of sound (SOS), integrated reflection coefficient (IRC), and broadband ultrasound backscattering (BUB); proprietary parameters have also been developed based primarily upon a combination of BUA and SOS aimed at estimating BMD [5–9]. Several researchers have shown that QUS parameters convey substantial BMD information [7,9–17]. Although quantitative ultrasound has been investigated for over 30 years now, the fundamental physics of ultrasound wave propagation through cancellous bone, and the resulting attenuation processes, are yet to be fully understood. Hence, ultrasound diagnosis of osteoporosis is still not accepted world-wide, despite having advantages of being non-ionizing, fast, affordable, portable, and easy to apply. Further, Hans et al. and Moayyeri et al. have

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shown that QUS measurements are indeed as powerful as DXA-derived BMD for predicting the risk of an individual sustaining an osteoporotic fracture [18–20].

A number of different mechanisms have been proposed to explain the attenuation observed in cancellous bone in addition to tissue absorption [21–23]. Bossy et al. has shown in numerical simulations that scattering alone can cause significant attenuation [24]. Further, Wear tested the hypothesis that longitudinal-shear wave conversion may be a significant source of attenuation in cancellous bone mimicking phantoms [25].

A major challenge in ultrasound signal analysis is the misinterpretation of measured signals due to overlapping waves. The impact of phase interference on the measured attenuation coefficient and phase velocity has been investigated by several researchers [26–36]. Anderson et al. provides a good summary and solved the inverse problem of overlapping fast and slow waves in plastic bone-mimicking phantoms and in cancellous bone by applying a Bayesian probability theory model [30,37,38]. Hoffman et al. successfully determined individual ultrasonic wave properties of overlapping waves in 8 human cancellous bone *in vitro* and found a correlation with bone porosity [39]. It was therefore suggested that knowledge about fast and slow wave parameters may improve bone quality assessment; however the full clinical relevance of the fast and slow wave properties remain unclear. Wear suggested applying the modified least-square Prony's Method (MLSP) in the frequency domain to decompose the two overlapping waves [34,40,41]. The MLSP method also effectively separated fast and slow waves; however the method has limitations for low signal to noise ratio; Wear suggesting that MLSP is most applicable for *in-vitro* investigations. In a recent study, Wear demonstrated that bandlimited deconvolution is an alternative and simpler technique to measure phase velocities and attenuation in solid bone mimicking plastic samples [42]. Bauer et al. [27] also reported anomalous properties in ultrasound bone studies (negative dispersion of phase velocity) that may be due to interference of two waves, which may be the fast and slow waves as predicted by Biot [43]. In a different study, Bauer et al. investigated the impact of phase cancellation on the transducer surface and interference of the wave in the field [44]. The phase cancellation at the transducer surface is a purely instrumental effect and causes irrecoverable energy loss, whereas interference in the field of overlapping waves relates to a redistribution of wave energy. Bauer concluded that the largest possible phase insensitive receiver should be applied in experiments to overcome artefacts in BUA measurements. A similar conclusion was also drawn by Cheng et al. (ovine femur *in-vitro*), Wear (human calcaneus *in-vitro* and *in-vivo*), and Petley et al. (human calcaneus *in-vivo*) [29,33,36,45], where phase sensitive (PS) and phase insensitive (PI) BUA measurements were performed, PS BUA being 17–40% higher than PI BUA; also suggesting that the aperture size of the receiver is crucial. In order to capture all of the ultrasound energy that has been redistributed due to interference and diffraction within the sample, the receiver should be at least equal to the size of the transmitter.

Langton has proposed that ultrasonic wave propagation may be approximated by parallel sonic rays and that the primary attenuation mechanism may be phase interference due to variations in transit time of the sonic rays as detected over the phase-sensitive aperture of the receive ultrasound transducer [46]. This has subsequently led to the development of Ultrasound Transit Time Spectroscopy (UTTS), with the potential to quantify both the bone volume fraction (BVF) and morphology of cancellous bone. The concept of Ultrasound Transit Time Spectroscopy has previously been introduced [46–48], where the propagation of ultrasound through a complex solid:liquid composite such as cancellous bone may be considered by an array of parallel 'sonic rays'. The transit time of each ray is defined by the proportion of solid (bone) and liquid (marrow) propagated, being a minimum (t_{min}) solely through solid and a maximum (t_{max}) solely through liquid. An ultrasound transit time spectrum ranging from t_{min} to t_{max}, may be defined describing the proportion of sonic rays having a particular transit time, $P(t_i)$, effectively describing lateral inhomogeneity of transit time over the surface of the receive ultrasound transducer. The resulting transit time spectrum therefore serves as the impulse response between input and output signals [48]. A previous comparison of experimentally-derived ultrasound signals for acrylic wedges exhibiting varying transit time inhomogeneity with computer simulation achieved agreement using Bland–Altman analysis ranging from 94.2% to 99.0% [47]. The aim of this study was to test the hypothesis that the solid volume fraction (SVF) of simplified bone-mimicking phantoms may be directly derived from an ultrasound transit time spectrum, even if the recorded ultrasound signal is subject to phase cancellation. We applied the active-set method deconvolution algorithm [48] to determine the ultrasound transit time spectra, from which the SVF was calculated. Transit time spectra and SVF values derived by both computer simulation (based on the parallel sonic ray concept) and experimental study were compared with values calculated from sample geometry.

2. Materials and methods

2.1. Samples

A range of simplistic solid:liquid models, as shown in Fig. 1, was manufactured using acrylic (Industrial Plastics Pty Ltd., Murarrie, QLD, Australia) and water as surrogates for bone and marrow respectively. The cylindrical shaped step-wedge models with a diameter of 25.1 mm varied in thickness of the solid component parallel to the direction of ultrasound propagation, hence exhibiting a range of transit time lateral inhomogeneities, ranging from minimal (single transit time) to multiple (20-level step-wedge). Model 'a' (water only) and 'b' (acrylic only) exhibit a single transit time component. Model c and d have an equal proportion of acrylic and water with interfaces that are normal and parallel to the direction of ultrasound propagation respectively. Model 'e' and 'f' have 75%:25% proportion of acrylic to water and vice versa. Model 'g'–'k' have step-wedge structures with 3, 4, 5, 10, and 20 steps of equal height and depth. The speed of sound in acrylic (v_a) was measured experimentally at 22.4 °C, being 2721 m/s, and the corresponding value in water (v_w) was calculated using Lubbers and Graff's formula [49], to be 1515 m/s.

2.2. Ultrasound measurements

Ultrasound experiments were carried out in ambient conditions using two 1 MHz, single element, planar, ¾″ diameter broadband transducers (Harisonics model I7-0112-G, Olympus NDT Inc., Waltham, MA, USA) in transmission mode. The −6 dB bandwidth was 0.78 MHz (0.67–1.45 MHz) with a centre frequency of 1.13 MHz and a pulse length 2.56 μs. The transducers were coaxially aligned with a fixed separation of 20.0 mm and immersed in a water bath. The transmitting transducer was energised by a 400 V spike from a pulser-receiver (Panametrics 5058PR, Olympus NDT Inc., Waltham, MA, USA). The ultrasound signals were acquired with 50 MHz sampling frequency by a 14-bit digitisation card (National Instruments PCI 5122, Austin, TX, USA). 1500 data points were collected equating to 30 μs. The ultrasound signal through water served as an experimental reference signal and as the input signal for both the computer simulation and digital deconvolution analysis. The effect of noise was considered in the computer simulation by using the experimental reference signal through water,

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