Ultrasonic Assessment of Bone Health

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Ultrasound has been used for clinical diagnosis for over 30 years, the most familiar application being foetal scanning. Current imaging devices exploit pulses of microsecond duration, having centre frequencies in the range 2-10 MHz, where the sub-millimetre wavelengths in soft tissue give spatial resolution of that order. The use of the higher frequencies improves resolution over that obtainable by earlier 1-3 MHz systems, but absorption is increased. This tends to reduce penetration, although the effect may be offset by improvements in signal processing or increased transducer output (which itself is limited by safety concerns, as discussed by Cunningham *et al* elsewhere in this issue [1]).

The trend has continued, with recent innovation in shallow-depth imaging in the skin and in ophthalmology, exploiting frequencies of up 100 MHz. Lower MHz frequencies are still valuable, however, not only for imaging but also for Doppler systems measuring blood flow. For example, quantitative blood flow information can be encoded using a colour scale and superimposed onto a tissue image, all in real time. Other innovations include the use of injected stabilised microbubbles to increase the acoustic reflectivity of blood; and the acoustic measurement of the elastic properties of tissue, for example, to identify tissue damage. Duck *et al* give an excellent overview [2].

Ultrasonic techniques for the non-invasive detection of osteoporosis have received considerable attention during the last decade. The clinical assessment of bone by ultrasound is based on measurement of the attenuation and the speed of sound. However, the technique is empirical, its accuracy has been questioned, and its inability to measure directly bone properties hinders its synergy with established X-ray diagnostic techniques. A system based on a propagation model for ultrasound in bone would alleviate these problems. Recent advances have been made in Southampton to provide such a model, as described in this article.

Osteoporosis

The normal adult skeleton consists of 206 bones, carrying out six different functions including support, protection and assistance with movement. Failure of this system is catastrophic, which in the elderly may severely impact on subsequent quality of life. The condition of the skeleton is maintained by a cycle of remodelling. Although bone is continually replaced, the rates of resorption and creation vary with age and disease. An imbalance can cause a reduction of bone mineral density (the volume or area density of calcium compounds in a given region of bone). This results in osteoporosis, a weakening of the skeleton, which causes 60,000 hip fractures each year in the UK, costing £940 million annually [3].

Osteoporosis affects not just the bone mineral density, but also the internal microstructure of bone. *Figure 1(a)* shows the anatomy of the foot and *Figure 1(b)* a cross section through the heel bone (the *calcaneum*). There is an outer sheath of compact 'cortical' bone, and a marrow-filled lattice of calcified strands (called *trabeculae*) that make up the core of 'trabecular' bone. Whilst bone mineral density accounts for roughly 60-70 % of bone strength, structure is the second most important factor, accounting for a further 10-20 % [4]. Owing to its high surface area and metabolic rate, trabecular bone displays the first signs of osteoporosis, when the trabeculae become thinner and the pores widen.

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Figure 1: (a) **The anatomy of the human foot, highlighting the calcaneus (heel bone) in red**

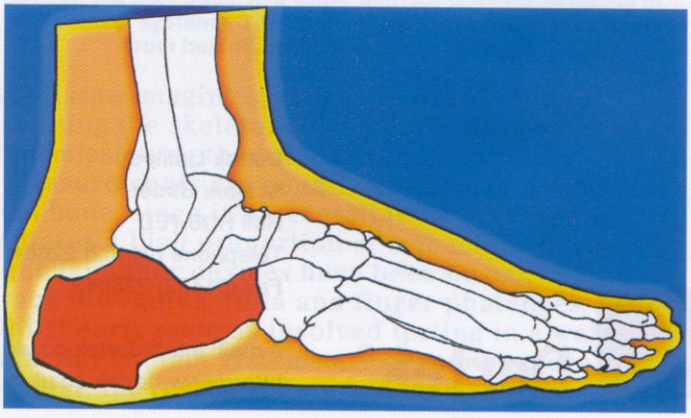
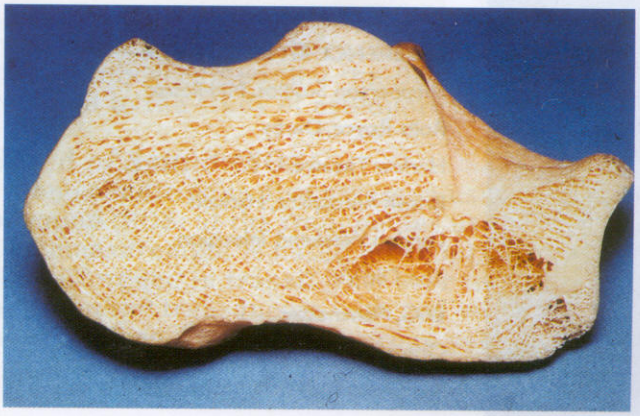


Figure 1: (b) **a cross-section of the calcaneus, showing internal porous structure**



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Drugs treatment, such as Hormone Replacement Therapy, can reduce the risk of a fracture if the disease is identified sufficiently early. The currently preferred method of diagnosis is Dual Energy X-ray Absorptiometry (DXA). These large, immobile and expensive devices use a low dose X-ray beam to measure bone mineral density, but crucially give no information of microstructure. Hence research has attempted to develop techniques to obtain complementary structural information which, when combined with DXA data, may improve fracture prediction.

The microstructure of trabecular bone lends itself to ultrasonic interrogation. A wide range of ultrasonic bone assessment systems is commercially available, collectively known as Quantitative Ultrasonography (QUS). The popularity of such systems has grown markedly in recent years, since QUS has a number of intrinsic advantages over DXA, such as low cost, lack of ionising radiation exposure, minimal regulatory requirements, and portability.

Quantitative Ultrasound

Ultrasound has been used to characterise the properties of bone from as early as 1949 **[5]**. Since bone has a high attenuation coefficient compared with soft tissue (about 10 dB/cm for bone and 0.5-2 dB/cm for soft tissue[1] at 1MHz), conventional

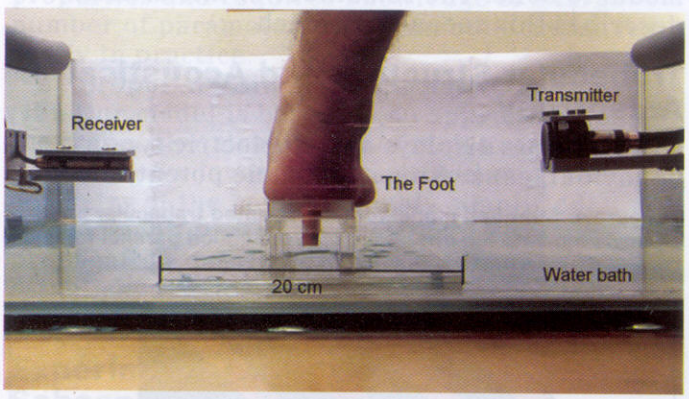

Figure 2: **The QUS transmission configuration. A signal, in the bandwidth 0.2 - 0.6 MHz is sent from transmitter to receiver through the heel bone, in a water bath for acoustic coupling in non-contact systems. The figure shows the right foot as seen from behind, without water in the bath.**

soft-tissue imaging systems are unsuitable for assessing the skeleton, and studies have used a transmission method *(Figure 2)*.

Measurements are usually performed on the heel bone, since it is accessible for testing and contains a high proportion of trabecular tissue, although other devices have been designed to probe the radius, tibia and finger phalanges. Whilst early systems involved testing in a water bath, dry contact systems are becoming more popular, for reasons of portability and hygiene.

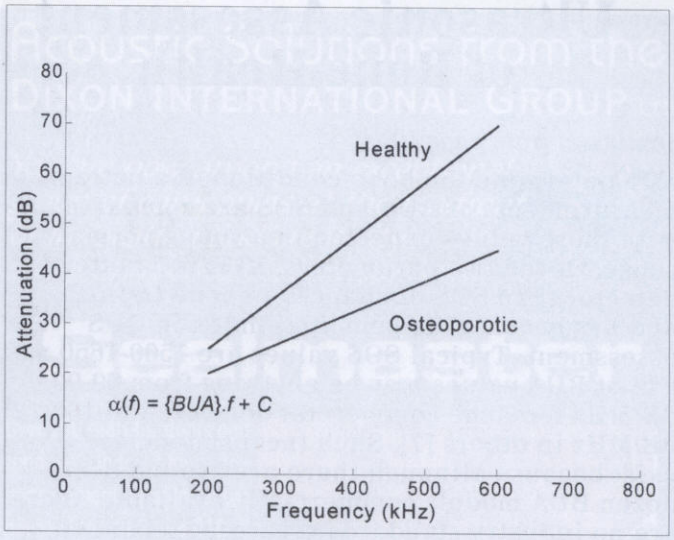

Figure 3: **Schematic illustration of the linear assumed between the attenuation and frequency of an ultrasonic pulse through the calcaneus, showing distinction between healthy and osteoporotic patients. BUA is the slope of the regression lines.**

The main ultrasonic parameters evaluated in QUS measurement are speed of sound and the frequency dependence of attenuation.

Broadband Ultrasonic Attenuation (BUA)

In 1984, Chris Langton introduced the Broadband Ultrasonic Attenuation (BUA) technique **[6]**. Whilst it now forms the basis of clinical QUS bone assessment, this empirical method is not entirely satisfactory.

The BUA technique essentially measures insertion loss, found by comparing the amplitude spectrum of an ultrasonic pulse through bone with that through a reference medium, typically water. The assumption is made that the attenuation, $\alpha(f)$, is a linear function of frequency, f, between 200 - 600 kHz, satisfying $\alpha(f) = \{BUA\}.f + C$, for constant, C. The term $\{BUA\}$ is the gradient in dB/MHz, evaluated by linear regression. Langton found that the *BUA* value of the spectrum was significantly lower in older women with osteoporotic fractures compared with young normals, a finding confirmed by later studies.

As a result, a standard graph **[7]** *(Figure 3)* is taken as the basis of the assessment of bone by BUA. *Figure 3* gives no indication of distribution in the population and, citing dB rather than dB/m, is not normalised for bone thickness. Despite this, and the fact that the linear relationship does not have any physical basis, it is widely accepted that the *BUA* gradient is relevant to the study of osteoporosis.

Speed of Sound (SOS)

Bone condition is also assessed using the speed of sound (SOS) at the frequencies used for BUA. The measurement is based on simply evaluating the difference in transit time over the distance between the transducers with and without the heel in place. Hence it is a group velocity.

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To determine the bone condition of a patient, measurements of BUA and SOS are compared with those values expected in a young normal range. Of the two parameters, BUA is a better detector than SOS of changes in bone tissue, and has become the principal index in QUS assessment. Typical SOS values are 1500-1650 m/s, whilst BUA values may be anything from 60-90 dB/MHz for some commercial devices, and 100-125 dB/MHz in others [7]. Such inconsistencies exist because although there are around a dozen BUA models commercially available, there are no industry standards regarding technical specifications.

Crucial to the role of QUS in the clinical management of osteoporosis is its performance in practice. To be of clinical value, an assessment system needs to perform at least one of three functions: to diagnose osteoporosis; to assess fracture risk; or to monitor the response to treatment. Strictly, diagnosis depends on evaluating statistically defined changes in density, a measurement that QUS cannot perform.

Fracture risk, however, can be assessed using secondary parameters (those not directly influencing bone strength), such as lifestyle factors, like smoking, or, in the case of QUS, the parameters BUA and SOS. Clinical trials have shown that heel QUS is able to predict the risk of hip fractures in elderly women [3], where it is a close second to DXA for this specific assessment. However, monitoring the response to treatment relies on the reproducibility of devices, and, owing to its poor performance in this regard, QUS is not recommended for use in this application.

Improving the performance of QUS involves understanding both practical factors and the information contained in the results. Measurement artefacts are not fully appreciated, so that for example, parameters are not typically normalised for heel thickness and paths through soft tissue are neglected. Furthermore, BUA and SOS are purely empirical measures that have not yet been firmly linked to physical parameters, such as bone strength or density. Establishing models for ultrasonic propagation in trabecular bone would be of significant value to the technology, and research in this area has been continuing at Southampton University for the last decade.

Application of Biot's Theory

Since trabecular bone is inhomogeneous, and the sizes of its features are close to wavelengths at the frequencies 200-600 kHz, the interaction between ultrasound and bone will be highly complex. Modelling ultrasonic propagation through trabecular tissue has been considered using porous media theories, such as Biot's theory [8].

Applications of Biot's theory to trabecular bone have enjoyed varying degrees of success. The theory predicts two compressional waves: a 'fast' wave, where the fluid (marrow) and solid (calcified tissue) move in phase; and a 'slow' wave, where fluid and solid move out of phase. Fast and slow waves were identified independently in bovine trabecular bone in the late 1990s by the current authors [9] and Hosokawa and Otani [10]. In both cases, the phase velocities of these waves were correctly predicted by Biot's theory.

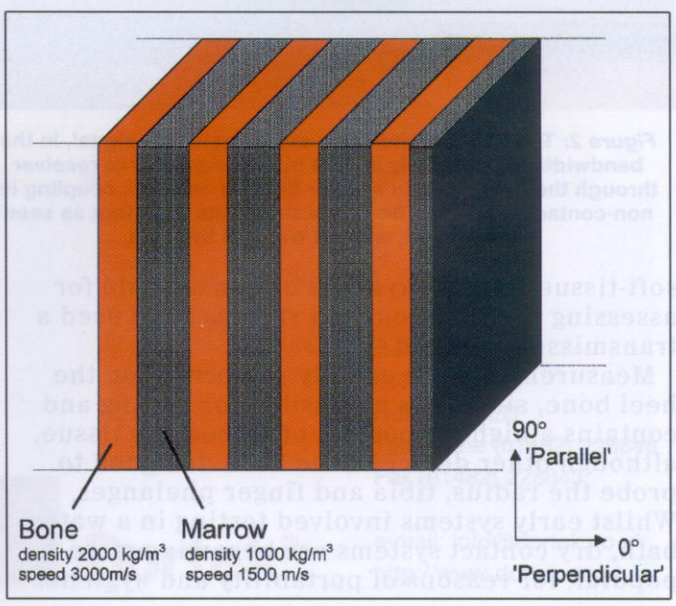
However, studies showing agreement between theoretical absorption and measured insertion loss have not been forthcoming. This is likely to be because whilst the model predicts viscous losses arising from motion of the pore fluid, it neglects factors such as interface reflections, diffraction of the ultrasonic field, the averaging effect of phase cancellation at the receiver, and crucially, scattering [11]. Research in Poland has recently incorporated scattering, believed to be the principal loss factor, into Biot's theory for application to bone [12], but this requires experimental validation.

Previous applications of Biot's theory assumed that trabecular bone is an isotropic medium; that is, its mechanical and acoustic properties are constant with direction. However, as described in the next section, trabecular bone is a highly anisotropic medium. Work at Southampton has investigated two approaches for providing an anisotropic propagation model: the incorporation of direction dependence into Biot's theory, either through an angular mass coupling term or anisotropic mechanical frame properties [11]; and the application of Schoenberg's geoacoustic model to bone. The remainder of this article describes this second approach.

Trabecular Structure and Acoustical Anisotropy

Bone tissue displays a piezoelectric-type behaviour, generating an electric potential when

Figure 4: **Stratified model for well-oriented trabecular bone. Arrows indicate the directions of propagation parallel to, and perpendicular to, the layers.**



under stress. It is believed this response stimulates growth, causing the trabeculae to grow along the trajectories of principal stress and forming distinctive patterns [13]. For example, the heel bone in *Figure 1(b)* displays a typical arch-like structure, from where the bone would meet the floor (bottom, left, referencing *Figure 1(a)*) to the joint with the tibia (top, centre). So characteristic are these patterns that the distinguishing architecture in the pelvises of 7-million-year-old hominoids has recently been cited as evidence that these apes walked upright [14].

The development of biomechanical models describing bone strength relies on the geometrical characterisation of this cellular architecture. In skeletal sites displaying dense, honeycomb structures, the mechanical behaviour of trabecular bone is typical of a cellular material, and techniques for analysing foams and honeycombs have enjoyed some success [15]. In bones where loading has one main direction, trabeculae are aligned in a dominant orientation and a simple layered structure of alternating bone-marrow plates can be used to model the geometry. The Young's modulus of the tissue is generally greater in the direction of dominant alignment than in orthogonal directions, and displays a degree of transverse isotropy.

Owing to such mechanical response, trabecular bone is acoustically anisotropic. The properties BUA and SOS vary with the direction of propagation, being highest for propagation in the direction of trabecular alignment [7]. A shortcoming of Biot's theory is that it does not model the anisotropic response of ultrasonic properties and requires knowledge of a large number of parameters that cannot be measured easily in practice.

We proposed a simpler, alternative approach [16]. Our model is based on an approximation of the trabecular structure as a series of parallel bone-marrow layers *(Figure 4)*. Although the geometry of the model is highly simplified, it is straightforward to investigate ultrasonic propagation in this system by applying the established Schoenberg theory of acoustic propagation in strata.

Experimental Validation of Schoenberg's Theory

Schoenberg's theory predicts the speeds of two compressional waves in a medium composed of periodically alternating fluid-solid parallel layers [17]. One period of a medium contains a layer of an elastic solid and a layer of an inviscid fluid. The speeds of these fast and slow waves are dependent on propagation direction through the layers, owing to a mass coupling effect between phases.

Figure 4 indicates two propagation directions, parallel and perpendicular to the layers. Parallel to the layers, waves travel independently through fluid and solid phases without interaction. However, coupling increases with angles, so that

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at perpendicular incidence, fluid and solid are locked together, and only one mode propagates.

We applied Schoenberg's model to an array of bone-marrow layers to predict wave speeds. Tests were performed on samples of trabecular bone from the bovine femur that contained a highly oriented microstructure. Ultrasonic pulses at 1 MHz were transmitted through the samples, and data was taken as the sample was rotated in the field at 5° increments. Two compressional waves were clearly seen for propagation parallel to the internal layers (90°), as shown in *Figure 5*. However, only one wave could be detected at low angles.

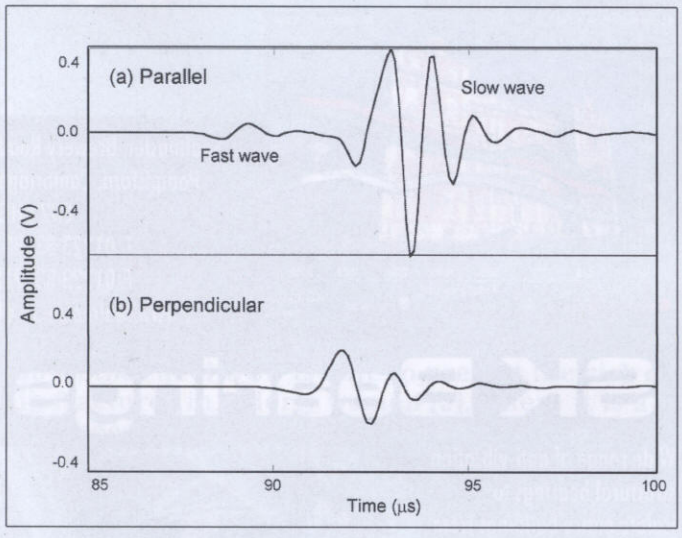

***Figure 5:* Time series of pulse through bovine bone (a) parallel to; and (b) perpendicular with main trabecular orientation.**

Good agreement was found between Schoenberg's predictions and data for the variation in the speed of sound with angle to the structure, as shown in *Figure 6*. Not only is the transition predicted from two waves at high angles ('parallel') to one wave at low angles ('perpendicular'), but the absolute sound speeds agree well for the most part with measurements taken in three different bone samples.

Implications of findings

This study demonstrated that ultrasound in trabecular bone containing a dominant trabecular structure behaves like that in a stratified array of bone-marrow layers. Although the stratified model clearly simplifies the trabecular architecture, the results provide a greater appreciation of the physical and dynamic forces involved, and, in particular, the work raises some interesting points about clinical assessment.

For example, it is an unwritten assumption that QUS measures only one propagation mode. The presence of two waves *in vivo*, which may challenge underlying concepts of the technique, has not been

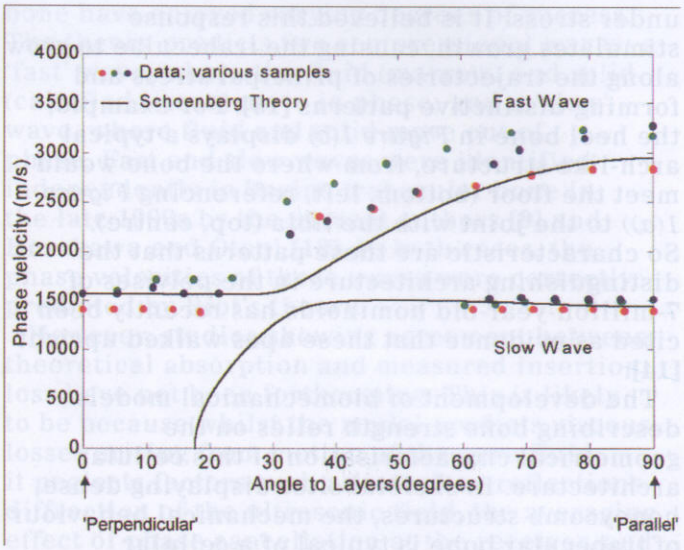

***Figure 6:* Phase velocities of fast and slow waves in bone versus angle of propagation to structure. Measured data from bovine femur in vitro is shown in coloured data points for three samples. Schoenberg's prediction is shown by the lines.**

investigated. QUS measurement may be performed in such a configuration that trabeculae in the heel are perpendicular to the direction of propagation (0° in *Figure 6*). In such a case, Schoenberg predicts that only the fast wave propagates, which may explain why two modes have not been observed in the heel. However, this issue is part of continuing research.

In the future, successful use of QUS in the management of osteoporosis may benefit from the development of systems with the ability to measure properties such as structure from ultrasonic parameters. Such devices would need to be based on a straightforward physical model. Whilst Biot's theory is too complex to be of notable value for inverting the acoustic data to estimate bone properties, the simpler Schoenberg model may have more potential. The success of such a model-based system would mark a breakthrough in QUS bone assessment.

The ultimate aim of current research programmes into osteoporosis is to find a technology that is cost-effective, reliable, accurate, and, eventually, widely available. When this happens, screening programmes for osteoporosis become viable, which will allow sufferers to be identified early enabling better targeting of drug treatment thereby reducing health care budgets and the incidence of osteoporosis-related fractures. The ongoing research in Southampton aims to contribute to understanding that may lead to such a development.

Acknowledgements

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