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QUO VADIS, ULTRASONICS OF BONE? PRESENT STATE AND FUTURE TRENDS

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Although it has been over 20 years since the first recorded use of a quantitative ultrasound (QUS) technology to predict bone fragility, the field has not yet reached its maturity. QUS have the potential to predict fracture risk in a number of clinical circumstances and has the advantages of being non-ionizing, inexpensive, portable, highly acceptable to patients and repeatable. However, the wide dissemination of QUS in clinical practice is still limited and suffering form the absence of clinical consensus on how to integrate QUS technologies in bone densitometry armamentarium. There are a number of critical issues that need to be addressed in order to develop the role of QUS within rheumatology. These include issues of technologies adapted to measure the central skeleton, data acquisition and signal processing procedures to reveal bone properties beyond bone mineral quantity and elucidation of the complex interaction between ultrasound and bone structure. In this presentation, we review recent developments to assess bone mechanical properties. We conclude with suggestions of future lines and trends in technology challenges and research areas such as new acquisition modes, advanced signal processing techniques, and models.

Keywords: bone, guided waves, finite difference time-domain, osteoporosis, quantitative ultrasound.

1. Introduction

Fragile bone are commonly (but not exclusively!) encountered in a disease called osteoporosis characterized by a decrease in bone mass and structural and material deterioration of bone, leading to increased susceptibility to fractures of the hip, spine and wrist. Osteoporosis is most common in women after menopause, but may also develop in men, and may occur in anyone in the presence of particular hormonal disorders and other chronic diseases or as a result of medications, for example long-term corticotherapy. Osteoporosis may significantly affect life expectancy (one-year mortality rates after hip fracture range from 15 to 20 percent) and quality of life. Osteoporosis is a major public health threat with extremely high costs to health care systems. Approximately

one in two women and one in four men over age 50 will have an osteoporosis related fracture in their remaining lifetime. The costs to governments measure in the billions of dollars annually, and these numbers are destined to increase, with as many as 6.3 million hip fractures predicted annually, around the world, by 2050. Clinicians and researchers alike are emphasizing the importance of early detection of osteoporosis and fracture prevention [1].

2. Bone quantitative ultrasound

Today, radiological (X-ray) measured bone mass serves as a surrogate for bone fragility, but fails to take into account other important aspects like material strength or structure. Mechanical waves such as ultrasound are intrinsically suited to probe mechanical properties and may perhaps have the best chances of all modalities to yield non-invasively an improved estimation of bone fragility combined with advantages like lack of ionizing radiation and cost-effectiveness. Ultrasound velocity and attenuation depends on the matter they are traveling through. For example, the more porous bones are, the better the penetration is (less attenuation) and the lower the velocity is. Consequently, bone tissue often is characterized in terms of ultrasound velocity and attenuation (or more specifically frequency-dependent attenuation).

Although the clinical potential of ultrasound for the investigation of bone fragility was recognized as early as in the 1950s where an ultrasound method was described for monitoring fracture healing [2], ultrasound was used little to investigate bone properties until the 1990s. The reason that ultrasound were not used before this date was because of immature technology and poor understanding of the interaction mechanisms between ultrasound and bone. In 1984 LANGTON *et al.* [3] took a step forward by discovering that the transmission of ultrasound through the heel could discriminate osteoporotic from non-osteoporotic women. He demonstrated that the heel of osteoporotic patients could transmit ultrasound waves better than that of an age-matched normal subjects. Subsequently, numerous experimental works demonstrated that the acoustic properties of the heel were tightly linearly and positively correlated to the bone volume fraction (or negatively correlated with the porosity) e.g. [4]. Since then many advances have been achieved by our group and others and a variety of different sophisticated technologies capable of measuring different skeletal sites such as the heel, fingers, wrist or leg have been introduced and evaluated. The evidence that ultrasound is a valid (radiation free and inexpensive) method for fracture risk assessment is first class [1]. In recent years, several devices received FDA approval that further opened the door to clinical acceptance and use. Bone ultrasound technology, termed QUS (Quantitative Ultrasound), gained a place in the armamentarium of modalities used to assess the skeleton.

3. QUS imaging

While the concept of measuring attenuation and velocity of ultrasound in bone has changed little since its inception, technology has evolved. Quantitative ultrasound imag-

ing of the skeleton, introduced by our group in 1996 was first applied to image the heel (Fig. 1) [5]. The image that is viewed results from the ultrasound passing through the skeletal site being inspected and interacting with a piezoelectric receiving transducer. Local values of the attenuation or of the wave speed are coded in grey (or color) level at the pixel in the image. As in plain radiography, the attenuation image formed is a "negative image" since brighter areas on the image indicate where lower levels of transmitted ultrasound reached the receiver. Today, we are able to generate real-time parametric images through the use of two-dimensional arrays of transducers [6]. Technological advances have provided clinicians with smaller, lighter, and very portable equipment such as that inexpensive device operated with four AAA batteries [7].

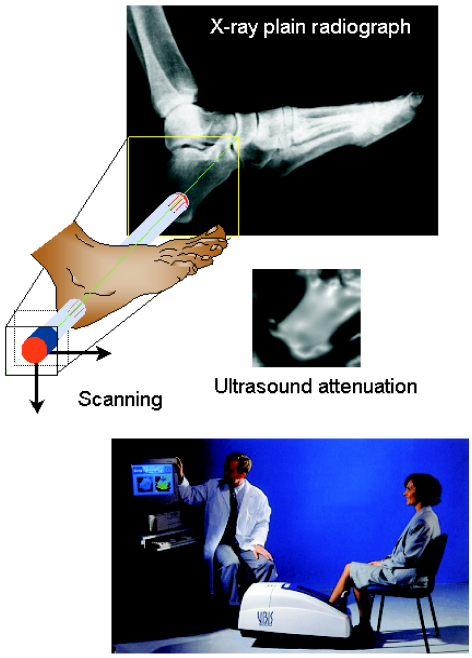

Fig. 1. *In vivo* ultrasound attenuation image of the heel. A pair of transducers are placed on opposite side of the heel. The image is obtained by scanning the heel and by recording the wave that passes through the heel at each scan point. The ultrasound image (the slope of the frequency dependent attenuation is coded in the image), compared to the X-ray plain radiography, shows high quality details.

An important limitation of QUS today is their limited access to peripheral skeletal sites only. One of the most significant recent technological advances is the a new QUS scanner developed by BARKMANN *et al.* [8] for direct assessment of skeletal properties at the proximal femur (hip) (Fig. 2). For X-ray based techniques measurements directly at the main osteoporotic fracture sites have proved to be superior to measurements in the peripheral skeleton. It is reasonable to also expect better hip fracture risk prediction for QUS assessment at the proximal femur compared to the heel. However, the complexity of the anatomy makes measurements at this site quite challenging.

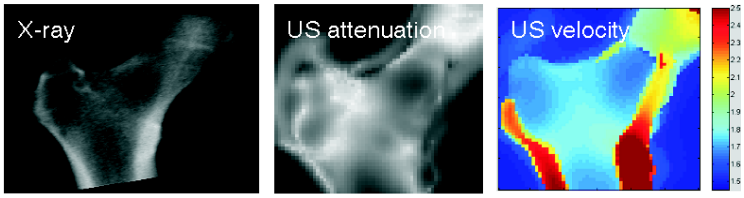

Fig. 2. *In vitro* QUS images of attenuation (middle) and sound velocity (rigth) of the femur compared to the X-ray bone mass image (left). Recent works have shown that ultrasound measurements could predict femoral bone mass with a reasonable accuracy [9]. Preliminary *in vivo* results have been recently published [8]. The left panel shows an image of the sound velocity. Interestingly, high velocity values are found at the boundary of the femur. We hypothesize that these high values correspond to the propagation of guided waves in the dense cortical shell that surrounds the femur. Measuring these guided waves (see next section) would provide invaluable information on the cortical shell properties [10].

4. Guided waves

More recently the emphasis of innovative QUS basic research has shifted towards cortical long bone measurements, such as the tibia (leg) or the radius (forearm). Like tube or pipelines inspected by non destructive ultrasonic testing methods, long bones can be probed by ultrasound waves produced in response to an impact (the ultrasound impulse) transmitted by a source to the bone through the soft tissue. The method has been adapted by our group to reduce artifacts caused by soft tissue [11] or by bone curvature [12] (Fig. 3). Waves propagate along the bone and their velocity, related to bone properties, is computed from measurements performed at distance from the source. Interestingly, long bones support the propagation of different kind of waves, such as surface or guided waves which contain relevant information on structural and material properties. Judicious choice of propagation modes over a suitable frequency range can be achieved and subsequent measurements of their velocities can reflect distinct aspects of bone quality [13, 14], hoping that they would appropriately reflect the bone quality status at the main fracture sites (e.g., hip or spine) and its changes associated with disease or treatment.

For example, in some devices, the measured signal is the first arriving signal (FAS). The physical nature of the fastest part of the signal depends on the ratio $Cort.Th/\lambda$. $Cort.Th$ being the cortical thickness and λ being the wavelength. In other approaches, the analysis of the signal is focused on a slower signal component which arrives after the FAS and has been identified as a guided wave mode.

First, we shall consider that the cortical thickness is much larger than the longitudinal wavelength in bone (i.e., high frequency regime). The theory predicts that the FAS corresponds to the so-called lateral wave, which propagates along the interface with a velocity v_{lateral} equal to the bulk compression wave velocity in bone $v_{\text{lateral}} = \sqrt{c_{33}/\rho}$, ρ being the mass density of cortical bone and c_{33} its stiffness coefficient (3: principal symmetry axis of the transversely isotropic medium corresponding to the long axis of the bone). The lateral wave can be easily detected by sensors placed at the surface of the soft tissue.

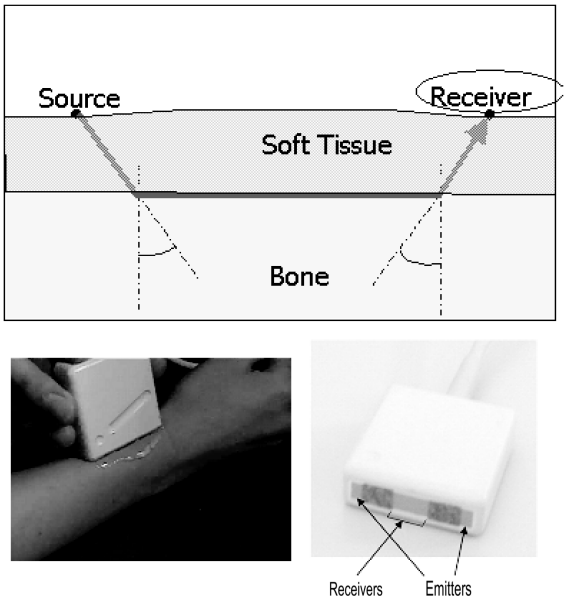

Fig. 3. Illustration of the technique implemented to measure long cortical bones. The measurement configuration consists in emitters and receivers placed on the skin on the same side of the inspected skeletal site, and the velocity is determined for an ultrasonic wave transmitted in the direction of the bone axis. Our group has developed a probe utilizing several ultrasonic transmitters to allow specific measurement sequences, the so-called bidirectional axial transmission technique, aiming at overcoming the effect soft tissue. In the bidirectional axial transmission approach, an ultrasonic pulse is transmitted along the bone surface in two opposite directions from two sources placed at both ends of a unique group of receivers. A simple combination of the time delays derived from waves propagating in opposite directions efficiently corrects automatically for soft tissue and for probe inclination with respect to bone surface.

A more realistic description must take into account the finite thickness of the cortical shell $Cort.Th$. For thin bone cortical layers or in the low frequency regime ($Cort.Th < 0.25\lambda$) the previous description is no longer valid. A guided wave mode instead of the lateral wave is excited in the cortex and contributes to the received signal. In case of a very thin layer the first arriving signal corresponds to the S_0 Lamb mode [15], which has an asymptotic phase velocity which can be written as a function of the stiffness coefficients [16]:

$$v_{S_0} = \sqrt{\frac{c_{33}}{\rho} \times \left(1 - \frac{c_{13}^2}{c_{11} \times c_{33}}\right)}. \tag{1}$$

This guided mode is slower than the longitudinal bulk wave. For plates of intermediate thickness ($Cort.Th \approx 0.25\lambda - 1.5\lambda$) the first arriving signal results from a complex pattern of interferences among different waves. As the cortical thickness-to-wavelength ratio decreases, the nature of the first arriving signal continuously changes between the long and short wavelength limits and the speed of sound decreases continuously (Fig. 4) [17]. The exact transition between the long and short wavelength limits

also depends on the acoustic anisotropy of cortical bone [17]. Figure 4 suggests that the FAS velocity conveys some information on the cortical thickness (i.e., velocity decreases with decreasing cortical thickness) which is a determinant of bone strength. FAS velocity measurements performed at multiple frequency [14] could potentially provide independent information on both cortical thickness and elasticity.

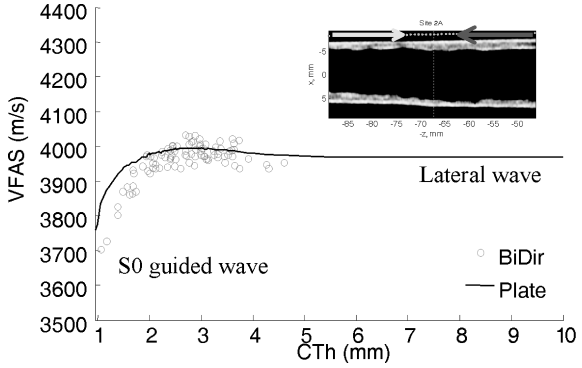

Fig. 4. Variation of the velocity of the FAS as a function of cortical thickness (Cort Th)-to-wavelength ratio. The continuous curve is from finite-difference time-domain (FDTD) computations on plate models with constant thickness [15], while the dots correspond to numerical simulations on realistic bone models with a geometry reconstructed from X ray tomography (see section Models), using a 1 MHz centre frequency signal and a bidirectional axial transmission configuration [11].

The possibility of measuring other wave modes than the first arriving signal in bone has been investigated recently [18–20]. An energetic contribution to the received signal has been observed (*in vitro* or *in vivo*) which has been identified (for *in vitro* cases only) as the antisymmetric guided wave (A0 mode for a plate model) or the fundamental flexural tube mode (F11 for a tube model) [19]. This mode is especially sensitive to the cortical bone thickness. Because this mode arrives after the first arriving signal and interferes with other contributions, special signal processing technique must be implemented for a reliable extraction and velocity estimate [19, 21]. Thus, if correctly identified and extracted by appropriate signal analysis, it may be suitable for data inversion processes [19], i.e., cortical thickness can be estimated from the determination of the guided wave mode propagation characteristics. Clinical assessment of long bones by this method is challenging, however, due to soft tissue on top of bone, because it may potentially increase the density of modes and affects differently their phase velocities and intensities. Identification and separation of modes measured *in vivo* remains challenging and requires further investigation.

QUS axial transmission techniques could find widespread clinical use to predict bone fragility not only in osteoporotic patients, but also in a wider context of bone diseases in female, male and pediatric populations. For example, preliminary studies suggest that this technique may be a useful method of assessing changes in bone health in preterm infants for whom X-ray technologies is unsuitable for such settings. An ultra-

sound wearable system for remote monitoring of the healing process in fractured long bones has also been reported [22].

5. Models

QUS techniques and implementations have been introduced into clinical practice despite the fact that the interpretation of QUS data is hampered by the structural complexity of bone. Interaction mechanisms between ultrasound and bone are still poorly understood. Modeling can be seen as a major need in order to drive future experiments, to optimize measurements, to integrate multiscale knowledge, to relate QUS variables to relevant bone biomechanical properties. Ultrasound propagation through bone is complex. It may involves different waves types, each with its own propagation characteristics. Ultrasound may propagate along curved paths, thus complicating the retrieval of the velocity. An accurate interpretation of ultrasound measurement results requires first a detailed understanding of ultrasound propagation with clear identification of the different waves and their exact propagation paths. The complex structure of bone significantly complicates the task of solving equations, though.

Recently developed computer simulation tools offer a fertile alternative to intractable theoretical formulations. Computer simulation will likely have its greatest impact by allowing the researcher to visualize the propagation of ultrasound trough the very complex three-dimensional bone structures, and by providing insight into the interaction mechanisms between ultrasound and bone. Simulators and computers may well become the primary tool for investigators to answer questions such as: how is the wave transmitted through the bone, what is the path followed by the wave? How does it interact with bone? What kind of wave is propagating? Computer simulations, illustrated on Fig. 5, have been applied to the problem of transmission through pieces of spongy bone (such as that found in the femur at the hip), and along or across long cortical bones such as the radius [17, 19, 23]. In every case the computer simulations provided valuable insight into the properties (e.g., nature and pathway) of the propagating waves. Typical snapshots of wave propagation (bottom) are presented for three distinct applications (top): 3-D spongious femur microstructure (left panel), 3-D human radius diaphysis (middle panel) and 2-D transverse cross-section of a human radius (right panel). The possibility of applying the 3-D FDTD approach to actual bone structures provides a valuable tool to study transmission of ultrasound waves through cancellous and cortical bone and to elucidate the interaction mechanisms between ultrasound and bone structures [17, 24, 25]. A 3-D snapshot of a 1 MHz quasi-plane wave propagating through a trabecular bone microstructure is shown on the left panel. A coherent ballistic plane wave is clearly seen, followed by a spatially incoherent scattered wave. Waves transmitted axially along the long axis of a human diaphysis are illustrated on the middle panel. Their nature are determined by the wavelength-to-cortical thickness ratio. Of particular interest are the leaky waves that can be detected with transducers placed on the skin using the so-called axial transmission technique. The right panel shows the transmission of a 1 MHz quasi-

plane wave in a transverse cortical experimental configuration. Circumferential guided waves propagating in the cortex are shown together with a wave front directly transmitted through the medullary canal.

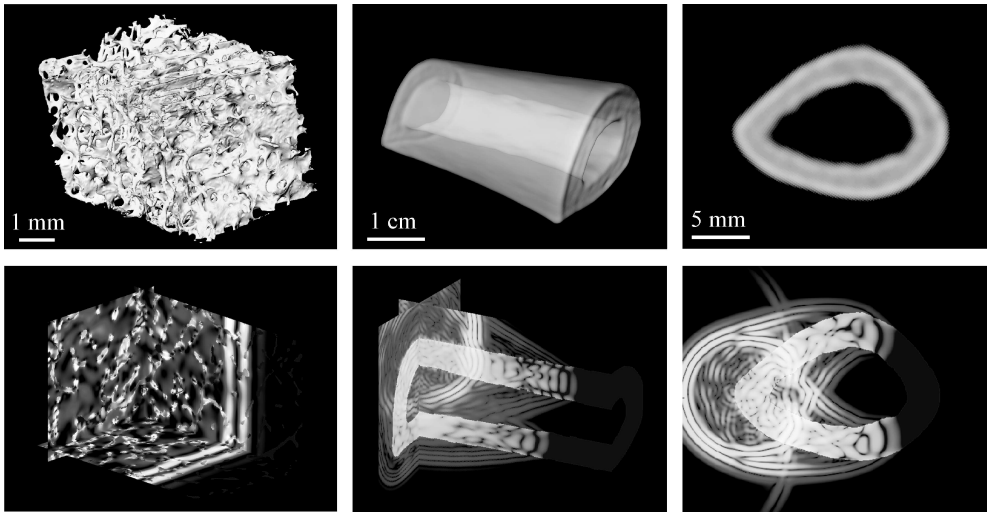

Fig. 5. The figure illustrates Finite-Difference Time-Domain (FDTD) simulations of wave propagation through bone specimens immersed in water. Such simulations are currently being performed on numerical models of bone by coupling a FDTD code with numerical three-dimensional (3-D) bone structures reconstructed from X-ray computed tomography data acquisitions.

Of noticeable interest is the computation of wave propagation through cancellous bone (Left panel of Fig. 6). Cancellous bone is a poroelastic and biphasic medium composed of an elastic skeleton (trabecular network) filled with a viscous fluid (bone marrow *in vivo*, or water *in vitro*). Theoretical models using the Biot theory [26–28] have been applied to cancellous bone [29–40] with some success. Briefly, the Biot's model predicts the existence of two longitudinal waves. However, Biot's theory presents several shortcomings in that it requires a large number of parameters that are not known with accuracy [41, 42] and is limited by its inability to accurately model the complex anisotropic and heterogeneous three-dimensional (3-D) bone microstructure. To overcome the technical difficulty of analytical modeling, we have recently turned to finite difference time domain (FDTD) computational bone models. The simulations predicted the existence of two compressional waves [25, 43] (Fig. 6). Fast waves are mostly related to a propagation mode mainly involving the solid phase, whereas slow waves are related to the fluid phase. Therefore, the arrival time (and also the amplitude) of the fast wave is simply determined by the velocity times the distance of propagation in bone tissue. This propagation length is in turn determined both by bone volume fraction and anisotropy of the structure. Short path length through the trabecular structure (either due to a weakly anisotropic structure or to a highly porous specimen) results in a fast wave front with low amplitude and arrival time too close to that of the slow wave. Therefore,

for short path length through the trabecular structure the fast wave should remain undetectable. The detection of the fast wave requires the propagation of the wave through a sufficient amount of trabecular structure, which depends on the structural orientation of the structure and on the bone volume fraction. These results provide deep insights into the propagation in poroelastic media and open interesting perspectives to link the characteristics of the fast wave to microstructural features.

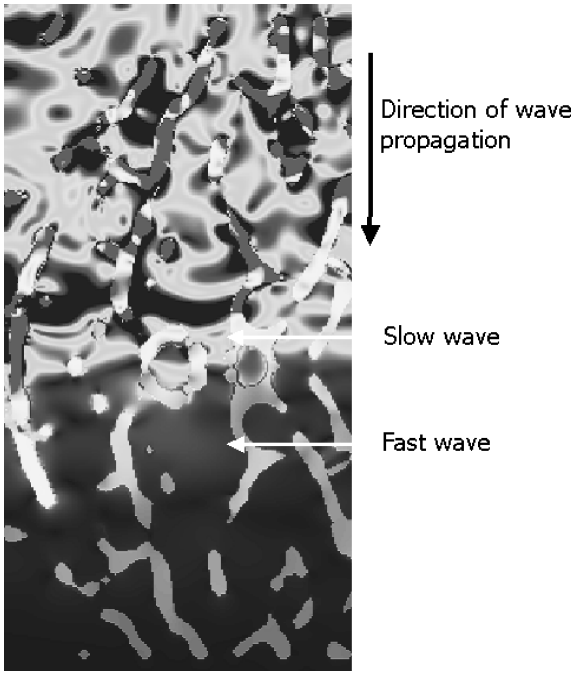

Fig. 6. Snapshot of the wave propagation through cancellous bone. The direction of wave transmission is indicated. Fast waves are mostly related to a propagation mode involving the solid phase, whereas slow waves are related to the fluid phase. A relationship was found between the least bone volume fraction required for the observation of non overlapping waves and the degree of anisotropy.

Computer simulation therefore resembles experiments in a virtual laboratory with independent control over each bone parameter. Virtual scenarios of osteoporosis for instance can be easily implemented, and used to form a comprehensive understanding of bone ultrasonic properties and their relation to bone biomechanical competence [44], help validate or refute theoretical approaches, and probe new experimental configurations.

6. Conclusion

Although the methodology for assessing bone properties using ultrasound is much less developed to date than with x-rays, the potential of ultrasound extends far beyond

the currently available techniques and is largely unexploited. Many new areas of investigation are in preliminary stages, though. Most active research is carried out in QUS to develop new measurement modes, access to the central skeleton (hip), exploit multiple propagation modes or extend the frequency range of the measurements. All these new developments should result in new QUS variables and systems, which coupled with adequate propagation models, would be able to provide information on material or structural properties other than density, and ultimately on osteoporotic fracture risk.

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