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# Quantitative Ultrasound Assessment of Cortical Bone Properties Beyond Bone Mineral Density

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1 Quantitative ultrasound assessment of cortical bone  
2 properties beyond bone mineral density

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6 **Abstract**

7 The development of quantitative ultrasound (QUS) technologies to mea-  
8 sure bone is motivated by the need to overcome the limitations of X-ray  
9 based methods, measuring bone mineral density (BMD) which is the gold  
10 standard to date for the diagnosis of osteoporosis. Because it uses me-  
11 chanical waves, the ultrasound modality is a particularly relevant means to  
12 probe bone mechanical resistance. The vast majority of QUS technologies  
13 commercialized to date merely aim to provide surrogate markers for BMD.  
14 During the past decade, innovative QUS approaches have emerged to assess  
15 bone beyond BMD. This may be achieved by (1) specifically assessing the  
16 cortical bone compartment, independently of trabecular bone, and (2) pro-  
17 viding intrinsic bone properties such as cortical bone thickness and material  
18 properties. One specific motivation is to estimate intracortical porosity, a  
19 quantity reflected in material properties. This article aims at an overview  
20 of recent QUS developments to measure cortical bone properties. We also  
21 draw a picture of the current knowledge on bone material properties of in-  
22 terest for bone QUS. We discuss the potential of ultrasound to provide novel  
23 biomarkers of bone health through the assessment of material properties.

24 *Keywords:* ultrasound; cortical bone; elasticity; porosity; thickness;  
25 imaging; velocity

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26 **Graphical abstract**

27 **Highlights**

- 28 • Bone fragility assessment would benefit from an accurate evaluation  
29 of cortical bone

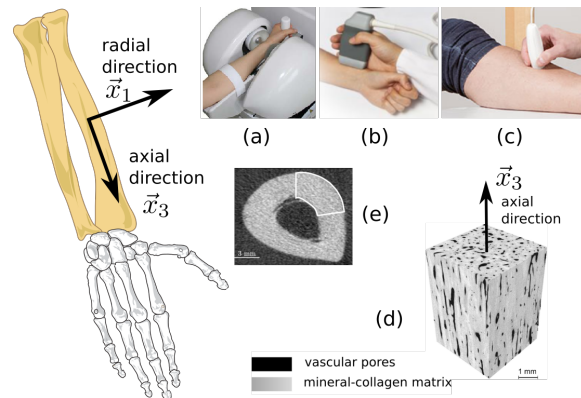


Figure 1: \*

**[Graphical abstract]** Bone anatomy and QUS measurement configurations. (a) Measurement in bone radial direction with a through transmission approach (courtesy of OYO Electric CO., LTD., Japan); (b) Measurement in bone axial direction with bidirectional axial transmission to measure guided waves (courtesy of AZALEE, France) ; (c) Measurement in bone radial direction with a pulse-echo approach (courtesy of Bindex, Finland) ; (d) image of cortical bone microanatomy obtained with synchrotron radiation microtomography showing the vascular porosity mainly oriented along the bone axis ; (e) X-ray image of a cross-section of the distal radius with a depicted region of interest for a typical QUS measurement with axial transmission.

- 30 • Innovative QUS technologies aim to measure intrinsic properties of  
 31 cortical bone
- 32 • Available technologies measure bone thickness and bulk wave velocities
- 33 • Intracortical porosity, a fingerprint of remodeling, can be deduced from  
 34 material properties
- 35 • Ex vivo documentation of material properties of pathological bone  
 36 tissues is lacking

37 **Reference for citation**

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 39 properties beyond bone mineral density. IRBM. 2018 Volume: 40 Issue: 1  
 40 Pages: 16-24

## 41 1. Introduction

42 Bone fragility associated to primary or secondary osteoporosis and the  
43 consequent risk of fracture is an important medical threat. Among the pop-  
44 ulation aged over 50 years old, one in three women and one in five men will  
45 suffer a fracture associated to osteoporosis. Nine million fragility fractures  
46 occurred annually worldwide at the beginning of the 21th century [1]. Frac-  
47 ture risk prediction is assessed based on clinical factors and, in the standard  
48 approach, dual energy X-ray absorptiometry (DXA) in order to assess bone  
49 mineral density (BMD). However, it is well accepted that BMD assessed with  
50 DXA has strong limitations, in particular it has a lack of sensitivity [2, 3],  
51 and DXA is a ionizing method.

52 Our bones are comprised of two types of porous tissues: cortical bone  
53 is the dense tissue that forms the outer shell of the bones; trabecular, or  
54 spongy, bone is the more porous tissue partly filling the bones. While  
55 for several decades, bone alteration in osteoporosis has essentially been de-  
56 scribed to be trabecular bone loss [4], a focus has been placed in recent years  
57 on cortical bone which has been recognized to also play a key role in bone  
58 resistance in particular at fracture sites such as the proximal femur [5, 6] and  
59 the distal radius [7]. Aging is associated with an increased cortical porosity  
60 and thinning of the cortical shell. In old age, 70% of all appendicular bone  
61 loss may arise from the cortical compartment [8]. It follows that including  
62 an accurate evaluation of cortical bone in skeletal status assessment could  
63 improve diagnosis and treatment monitoring.

64 Cortical bone mechanical properties depend on the properties of the pore  
65 network (volume fraction of pores or, shortly, the porosity, and microarchi-  
66 tecture) and the properties of the extracellular mineralized matrix (shortly,  
67 matrix) surrounding pores. Pathologies, aging, and treatments may alter  
68 matrix material properties through modifications of collagen and mineral  
69 [9, 10, 11, 12] and the pore network [13, 8, 11]. In the last years, corti-  
70 cal bone porosity has been increasingly recognized as a fracture risk factor  
71 [14, 15, 16].

72 Cortical bone thickness (CTh) is also a critical quantity for the stability  
73 of a bone during daily activities and in falls [5, 17]. A reduction of CTh is  
74 usually associated to an increase of porosity [16].

75 Techniques to assess specifically the cortical compartment of the skele-  
76 ton have been developed recently. These include X-ray computed tomog-  
77 raphy (CT) [18], indentation to specifically probe bone matrix [19], and  
78 quantitative ultrasound (QUS) methods. X-ray CT is extensively used for  
79 bone quantitative imaging, but essentially in clinical research. The most

80 advanced X-ray CT technique is high-resolution peripheral computed to-  
81 mography (HR-pQCT), a method available since 2004. It is a 3-D imaging  
82 technique, that allows a quantitative analysis of the cortical and trabecular  
83 bone compartments with a physical resolution of the order of 100  $\mu\text{m}$ . It  
84 yields estimates of bone density, microarchitecture, and geometry. It can be  
85 used to measure CTh and, to some extent, porosity, at the distal radius and  
86 tibia. This modality, however, like conventional CT, will unlikely be used as  
87 a widespread diagnostic tool for osteoporosis due to cost issues and ionizing  
88 radiations. The focus of the present review is on bone QUS methods to  
89 measure cortical bone.

90 In the past three decades, researchers have developed QUS methods to  
91 measure trabecular and cortical bone [20, 21] motivated by the need to over-  
92 come the limitations of DXA and provide a non ionizing, portable, easily  
93 accessible, and affordable diagnostic tool for osteoporosis. The ultrasound  
94 modality is thought to be a particularly relevant means to probe bone health  
95 because it uses mechanical waves which are inherently sensitive to mechan-  
96 ical properties contributing to bone overall resistance.

97 One strategy in bone QUS research has long been to provide ultrasound  
98 variables, based on attenuation, velocity or backscatter measurements, as  
99 surrogate markers for BMD, the gold standard to date for the diagnosis of  
100 osteoporosis. The vast majority of bone QUS technologies commercialized  
101 and used in clinical studies since the 1990's fall into this category. This  
102 includes the earliest and best-validated clinical bone ultrasound devices [22]  
103 measuring in transmission the heel bone (mainly composed of trabecular  
104 bone), as well as recently developed pulse-echo techniques targeting different  
105 skeletal sites such as the spine and hip [23, 24]. The ultrasound surrogate for  
106 BMD predicts fracture risk, although, compared to DXA, it has not shown  
107 its superiority [25, 20] to date.

108 Another strategy in bone QUS research has been to measure *intrinsic*  
109 bone properties that convey information beyond BMD, such as CTh and  
110 material properties, such as bulk wave velocities. In that vein, approaches  
111 have been proposed during the past decade such as pulse-echo [26] and axial  
112 transmission [27] techniques which we cover in this review. The development  
113 of such QUS approaches requires a priori knowledge of physiological values of  
114 bone material properties and of their expected ranges variation in different  
115 pathologies.

116 This paper reviews the recent progress in QUS approaches aiming at the  
117 evaluation of bone fragility through the measurement of the thickness and  
118 material properties of cortical bone. We also draw a picture of the current  
119 knowledge on bone material properties of interest for in vivo ultrasound eval-

120 uation. After this introduction as background, we review in section 2 cortical  
121 bone microanatomy and material properties. Section 3 presents QUS ap-  
122 proaches to measure cortical bone. In Section 3.2, we account for the recent  
123 research aiming at a concurrent assessment of cortical bone anatomy and  
124 material properties. In Section 4, we discuss the potential of ultrasound to  
125 provide novel biomarkers of bone health through the assessment of material  
126 properties.

## 127 **2. Cortical bone tissue**

### 128 *2.1. Anatomy*

129 At its highest level of hierarchical organization, i.e., the millimeter (mm)-  
130 scale, or mesoscale [28], cortical bone can be considered as a two-phase  
131 composite material: a mineralized collagen matrix pervaded by a porous  
132 network [29] (Fig. 2(d)). Bone mechanical properties are determined by the  
133 properties of the two phases: (1) pore structure and relative volume, and  
134 (2) matrix composition and microstructure.

135 At the nanometer scale, collagen molecules form fibrils which are progres-  
136 sively mineralized forming the elementary blocks of the matrix. Arrays of  
137 mineralized collagen fibrils assemble into lamellae to form cylindrical struc-  
138 tures called osteons, which are the most prominent motifs at the highest  
139 microstructural level in cortical bone. In long bones, osteons align roughly  
140 parallel to the axis of the diaphysis (central tube-like part of long bones)  
141 and to the bone outer surface [30]. The vascular pore network is comprised  
142 of the roughly cylindrical Haversian canals (median size  $\sim 50 \mu\text{m}$ ) occupy-  
143 ing the center of osteons, connected transversely by the Volkman's canals.  
144 Unbalanced bone remodeling occurring, e.g., in aging tend to change the  
145 porosity and the morphology of the pores. While pores occupy more or less  
146 5% of the bone material volume before 40 years old, after 40, differences are  
147 reported between women and men, the inter-individual variations increase,  
148 and, in women, the average porosity may reach about 15% [13, 31]. Also,  
149 porosity is known to be spatially heterogeneous within a bone, e.g., around  
150 the circumference and in the radial direction [13, 32, 33].

### 151 *2.2. Notations*

152 Anatomical directions in a bone diaphysis are conveniently associated to  
153 a Cartesian reference frame where directions 1, 2, and 3 stand for radial,  
154 circumferential, and axial (along the diaphysis) directions (Fig. 2).

155 Ultrasound propagation in bone comprises the propagation of dilata-  
156 tional and shear waves and is affected by material anisotropy leading to a

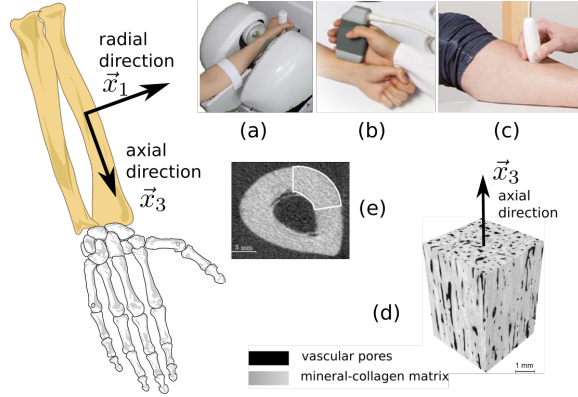


Figure 2: Bone anatomy and QUS measurement configurations. (a) Measurement in bone radial direction with a through transmission approach (courtesy of OYO Electric CO., LTD., Japan); (b) Measurement in bone axial direction with bidirectional axial transmission to measure guided waves (courtesy of AZALEE, France) ; (c) Measurement in bone radial direction with a pulse-echo approach (courtesy of Bindex, Finland) ; (d) image of cortical bone microanatomy obtained with synchrotron radiation microtomography showing the vascular porosity mainly oriented along the bone axis ; (e) X-ray image of a cross-section of the distal radius with a depicted region of interest for a typical QUS measurement with axial transmission.

157 direction-dependent speed of sound. Speed of sound is the square root of  
 158 an elasticity-to-mass density ratio. We recall that the elasticity law may be  
 159 written using Voigt notation as  $\sigma_i = C_{ij}\epsilon_j$ , where  $\sigma_i$  and  $\epsilon_j$  are components  
 160 of the stress and strain vectors respectively, and  $C_{ij}$  is the stiffness ma-  
 161 trix. Stiffness constants  $C_{ii}$  ( $i = 1 \dots 3$ ) correspond to longitudinal loadings  
 162 (of traction-compression type) along the different anatomical directions,  $C_{ii}$   
 163 ( $i = 4 \dots 6$ ) are the shear moduli, and  $C_{ij} = C_{ji}$  ( $i \neq j$ ) correspond to mixed  
 164 mode loadings. Engineering moduli, i.e., Young's moduli and Poisson ra-  
 165 tios are defined as combinations of stiffness constants [34]. In the following,  
 166 the bulk wave velocity (BWV) of dilatational waves,  $\sqrt{C_{11}/\rho}$ , and  $\sqrt{C_{33}/\rho}$ ,  
 167 where  $\rho$  is the mass density, are denoted respectively radial BWV and axial  
 168 BWV.

### 169 2.3. Elastic anisotropy

170 Cortical bone is most often described as an orthotropic material, that  
 171 is, the material has a plane of symmetry associated to each anatomical di-  
 172 rection. Such a material is characterized by nine distinct elastic moduli.  
 173 Where orthotropy is weak as in the central portion of the diaphysis, a trans-  
 174 versely isotropic material model, characterized by five moduli only [35, 36],

175 is usually assumed. In long bones, the typical anisotropy ratio between lon-  
176 gitudinal coefficients in the axial and radial (or circumferential) directions  
177 is between 1.3 and 2.5 [35, 37]. Anisotropy of cortical bone is due to both  
178 the preferential orientation of the vascular pores and the elastic anisotropy  
179 of the mineralized matrix due to the orientation of the mineralized colla-  
180 gen fibers. Theoretical studies have shown that bone mesoscale anisotropy  
181 mostly stems from the anisotropy of the matrix, the preferential orientation  
182 of the pores leading to moderate values of anisotropy ( $C_{33}/C_{11} \sim 1.1-1.3$   
183 depending on the pore volume fraction) when the mineralized matrix is as-  
184 sumed to be isotropic [38, 39, 40].

#### 185 *2.4. Bone material properties*

186 A large number of ex vivo studies have reported elasticity values in cor-  
187 tical bone. The average Young's modulus along the diaphysis is typically  
188 around 14-20 GPa [41, 42, 37]. The average Young's modulus perpendic-  
189 ular to the diaphysis is around 11 GPa [37] but is much less documented.  
190 The average shear modulus corresponding to a torsion experiment around  
191 an axis parallel to the diaphysis is about 4-6 GPa [42, 37].

192 The mass density of cortical bone ranges typically between 1.6 and  
193  $2 \text{ g.cm}^{-3}$ . The variations of mass density are due to a combination of vari-  
194 ations of the bone volume fraction in a volume of interest (i.e., the bone  
195 is more or less porous) and the variations of the mass density of the ex-  
196 tracellular mineralized matrix. The latter are usually small because the  
197 volume fraction of mineral in mature bone remains relatively constant[43] .  
198 It follows that in practice mass density and porosity are highly correlated.  
199 The above interval ( $[1.6-2] \text{ g.cm}^{-3}$ ) approximately corresponds to a range  
200 of porosity between 30% (extremely high porosity for cortical bone) and a  
201 few percents. In this range of density values, the elastic constants vary of  
202  $\pm 30-50\%$  around their nominal values [37] (Fig. 3).

203 In a large number of ex vivo studies, BWVs in cortical bone specimens  
204 have been measured together with mass density in order to derive elastic-  
205 ity [44]. However, the BWVs values were not reported as such. Overall,  
206 compared to elasticity, BWV is much less documented. Eneh et al. [45]  
207 measured radial BWV ex vivo on parallelepiped samples of femoral bone  
208 from 18 donors and found 3202 m/s ( $\pm 77$ )(Fig. 4). Lefevre et al. [46] mea-  
209 sured radial and axial BWVs ex vivo in samples of fibula from 16 donors and  
210 found, respectively, 3137 m/s ( $\pm 486$ ) and 3994 m/s ( $\pm 178$ ). Grondin et al.  
211 [47], combining measurements in several quadrants of the femur of 4 donors  
212 found 3976 m/s ( $\pm 72$ ) for axial BWV. Mathieu et al. [48] investigated the  
213 radial variation of axial BWV in 11 femurs and found 3586 m/s ( $\pm 255$ ). In



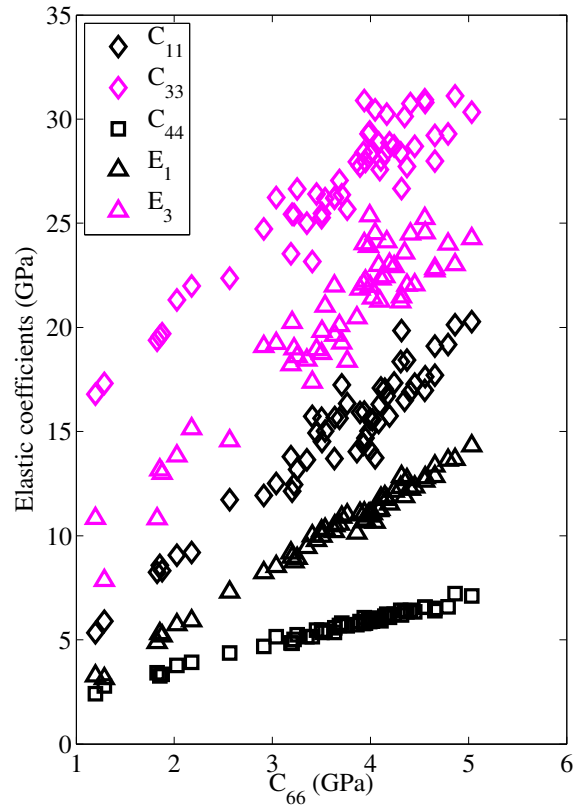


Figure 3: This figure, reproduced from [37], illustrates the ranges of variations of elastic coefficients (ex vivo measurements). Stiffness and engineering coefficients of 55 cortical bone specimens from the tibia, are plotted as a function of  $C_{66}$  to illustrate the interdependency of the different elastic coefficients. The range of mass density values is [1.6-2.0]  $\text{g}\cdot\text{cm}^{-3}$  for the different specimens.

214 vivo, Greenfield et al. [49] combined radiographic measurement of radius  
 215 thickness and pulse echo data to determine BWV in the radial direction,  
 216 they found (mean  $\pm 1.5$  standard deviation) 3311 m/s ( $\pm 307$ ) in men and  
 217 3359 m/s ( $\pm 297$ ) in women.

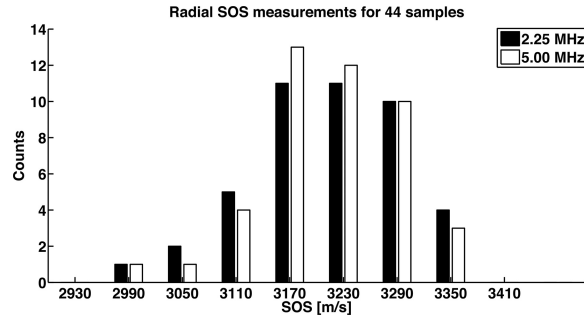


Figure 4: Reproduced from [45]. Histogram (numbers represent the center of bins that are 60 m/s in width) of the average values of radial bulk wave velocity (denoted SOS for 'speed of sound' in the figure) in 44 cortical bone samples from the femur diaphysis. The black and white bars represent radial BWV measured at 2.25 and 5.00 MHz, respectively.

218 As explained in sec 3, the design of future bone QUS methods to measure  
 219 material properties rely on reference data at the typical measurement sites  
 220 (radius, tibia). Some ex vivo studies have provided values for cortical bone  
 221 material properties such as elasticity, density and BWVs. However, the large  
 222 majority of this data was obtained from the diaphysis of the femur, which is  
 223 not a site measured with QUS, and, to a lesser extent, from the tibia. Little  
 224 data exists on radius bone due to the difficulty to measure small samples.

225 The available data was obtained on cadaveric bones, usually from el-  
 226 derly donors without documentation on the existence of bone pathologies.  
 227 During childhood, there is a well documented effect of age on bone mineral  
 228 density [50]. The changes over age of material properties are not covered  
 229 in the present review, although a bone QUS method can be dedicated to  
 230 measure children's bones.

231 To conclude, elastic properties and BWVs at radius and tibia need to  
 232 be better documented. In particular, it is not clear whether or not bone  
 233 material has distinct characteristics at these two sites (tibia, as opposed to  
 234 radius, is a weight-bearing bone) and if these sites are comparable to the  
 235 femur for which much more data is available. A better documentation of  
 236 the tibia and radius bones may be obtained with resonant ultrasound spec-  
 237 troscopy (RUS) [51, 52] a technique that allows retrieving the full stiffness  
 238 tensor from small-sized rectangular parallelepiped specimens.

### 239 3. Cortical bone quantitative ultrasound

240 We review below cortical bone QUS approaches aiming at the measure-  
241 ment of cortical bone thickness (CTh) and material properties. These QUS  
242 approaches are essentially developed for the radius and tibia [53] because  
243 these sites are easily accessible to ultrasound. The radius, but not the tibia,  
244 is an osteoporotic fracture site. Osteoporosis is a systemic disease, accord-  
245 ingly, measuring bone at any site is expected to have a clinical value, which  
246 has been proven with several approaches implemented at the heel, phalanx,  
247 tibia and radius.

248 In general, the measurement of CTh with ultrasound in vivo relies on  
249 an a priori knowledge, or a joined measurement, of one or several material  
250 properties. When measuring bone in the radial direction with a pulse-echo  
251 method (Fig. 2(c)), the ultrasound raw data, in terms of time-of-flight, cou-  
252 ple information on material properties (BWVs) and anatomy (CTh). With  
253 the axial transmission method, measuring the propagation of guided waves  
254 in the cortical envelope of the diaphysis (Fig. 2(b)), information on bulk  
255 wave velocities and CTh are also coupled (except in the limit case of a suf-  
256 ficiently large CTh and high frequency, in which case a lateral wave can be  
257 measured [54], giving access directly to the axial BWV without requiring  
258 the knowledge of thickness).

259 At QUS measurement sites, CTh shows a large range of values across  
260 individuals: typically 1 to 4 mm in radius and 1.5 to 5 mm in tibia [26, 55].  
261 In contrast, the range of variations of material properties is smaller, e.g.,  
262 typically, the mass density varies between 1.8 and 2 g.cm<sup>-3</sup>, and the BWVs  
263 and elastic coefficients may respectively vary of  $\pm 10\%$  and  $\pm 50\%$  around  
264 an average value. Because it is intrinsically difficult to retrieve concurrently  
265 several bone characteristics (namely CTh and material properties), to date,  
266 clinical implementations of QUS approaches only provide CTh assuming  
267 fixed values of material properties. Several approaches are under develop-  
268 ment to overcome this limitation.

#### 269 3.1. Current approaches

270 Karjalainen et al. [26], following Greenfield et al. [49] and Wear [56]  
271 implemented a pulse-echo method (Fig. 2(c)) to measure CTh at the tibia  
272 and radius using a fixed value of the radial BWV (3565 m/s). This value  
273 was chosen such that CTh determined from the QUS measurement matches  
274 the reference CTh obtained from HR-pQCT in healthy volunteers.

275 Otani et al. developed a method to measure the distal radius in through-  
276 transmission, i.e., the wrist is placed between a pair of confocally aligned

277 transducers, [57] (Fig. 2(a)). Ultrasound passes through both the lateral and  
278 medial cortical layers and through the trabecular bone in the metaphysis.  
279 Assuming a layered model of bone and some fixed material properties (radial  
280 BWV in cortical bone is set to 3300 m/s), the method yields, among other  
281 parameters, the sum of the cortical thicknesses at the inlet and outlet sides  
282 of the the US beam.

283 So-called axial transmission measurements involve guided waves prop-  
284 agating in the cortical layer in the direction of the bone axis (Fig. 2(b)).  
285 Guided waves propagation is highly sensitive to variations of CTh [27, 58].  
286 The waveguide thickness is retrieved by resorting to an optimization al-  
287 gorithm to solve an inverse problem. Precisely, the cortical bone layer is  
288 modeled as a plate of given (fixed) material properties and unknown thick-  
289 ness (CTh), to be determined by fitting the simulated ultrasonic behav-  
290 ior of the plate to experimental data. Moilanen et al. [59] demonstrated  
291 on ex vivo radii that CTh can be retrieved from the signal of a 200 kHz  
292 guided wave; in this work, bone material was assumed isotropic with fixed  
293 properties (BWV=4000 m/s). In a subsequent study, Vallet et al. [55] ex-  
294 ploited several guided modes [60] to retrieve CTh using US signals centered  
295 at 1MHz and transverse isotropic fixed properties (radial BWV=3024 m/s;  
296 axial BWV=3753 m/s).

297 During the last few years, the first clinical studies with the above ap-  
298 proaches have been conducted. CTh was found to be different in fractured  
299 versus non fractured patients, all with impaired kidney function [61]. Sai  
300 et al. [57] observed the expected decrease of CTh with age in an healthy  
301 population and the higher thickness of males compared to females. The  
302 pulse echo method of Karjalainen et al. [26], combining measurement of  
303 CTh and patient's characteristics, was shown to predict femoral neck BMD  
304 with good accuracy [62] and to discriminate patients with hip osteoporosis  
305 from controls [63, 24].

### 306 *3.2. Future of cortical bone QUS*

307 In all the above-mentioned approaches, cortical bone material properties  
308 are assumed to be identical for all subjects. This a limitation as tissue  
309 properties may vary between individuals and between sites (section 2). Not  
310 only this likely impairs the accuracy of the determination of CTh but also  
311 material properties themselves may give a valuable additional information  
312 on bone quality. In particular, material properties are strongly related to  
313 porosity, which is a recognized fracture risk factor [64, 15] (see sec. 4).

314 *3.2.1. Innovative methods*

315 One perspective for cortical bone QUS, based on existing approaches, is  
 316 to couple the determination of CTh and that of material properties. This  
 317 can be achieved with several approaches. In pulse-echo mode, methods using  
 318 a transfer function approach [65, 66, 67] could in principle be designed to  
 319 retrieve BWVs, density, attenuation, and CTh exploiting the times-of-flight  
 320 and amplitudes in the reflected signals. The multimode axial transmission  
 321 technique allows retrieving CTh and material properties or porosity, which  
 322 has been demonstrated ex vivo [68, 69, 70].

323 Obtaining ultrasound images of the internal structure of cortical bone is  
 324 another exciting perspective. Conventional ultrasound scanners are used in  
 325 clinical practice to image the outer surface of bones allowing for the diagno-  
 326 sis of bone fractures [71]. However, these ultrasound systems fail to reveal  
 327 the internal structure of bones because (1) the algorithm used to construct  
 328 the image assumes that ultrasound follow a straight path and that BWVs  
 329 do not vary along the path; (2) attenuation in cortical bone is relatively  
 330 large; and (3) important energy loss occur at the soft tissue-bone interface  
 331 caused by the large acoustic impedance mismatch. Using wave scattering  
 332 theory to model the wave path, Zheng et al. [72] obtained ex vivo an image  
 333 of the cortical layer of a bovine femur. Taking advantage of the tremendous  
 334 performance improvement of hardware electronics in ultrasound scanners in  
 335 the last years and developing a dedicated image reconstruction technique,  
 336 Renaud et al. [73] have recently obtained in vivo quantitative images of the  
 337 cortical layer of human radius and tibia (Fig. 5). The velocity of bulk dilata-  
 338 tional waves in the different anatomical directions is recovered by combining  
 339 a measurement of the lateral wave and optimizing image quality.

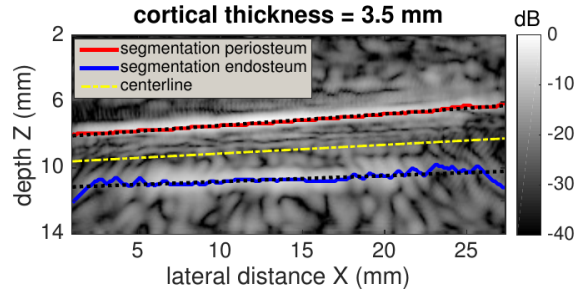


Figure 5: Reproduced from [73]. Ultrasound image of the cortical layer of a radius in vivo. Red and blue lines correspond to the periosteum and endosteum. Straight lines (dotted black line) approximate the interfaces. The cortical thickness, defined as the mean distance between these lines is found to be 3.5 mm for this acquisition and is in agreement with the thickness measured with HR-pQCT.

340 Lasaygues et al. have proposed to reconstruct a quantitative image of  
341 an entire transverse cross-section of a long bone with a tomography setup,  
342 using scattering theory and Born approximation [74] or using a full waveform  
343 approach [75].

### 344 3.2.2. *Models of material properties for cortical QUS*

345 Depending on the QUS measurement approach and the type of waves  
346 involved (shear and dilatational waves in different anatomical directions),  
347 more or less material parameters are involved in the processing of ultrasound  
348 signals. While only the radial dilatational BWV is involved in pulse-echo  
349 methods, no less than four material parameters may be involved in axial  
350 transmission configuration (e.g., one BWV and three elastic anisotropy ra-  
351 tios [68] ). The latter parameters are the quantities directly accessible from  
352 a measurement. In the methods implemented for clinical applications, nor  
353 mass density nor elastic coefficients can be inferred without resorting to a  
354 model of bone material properties (e.g.,[40] ) relating these quantities and  
355 those directly accessible from a measurement.

356 A priori knowledge of bone material properties is mandatory to solve  
357 the coupled problem of the determination of CTh and material properties.  
358 Such information is all the more important that the number of parameters to  
359 retrieve is large. It has been pointed out that the different elastic coefficients  
360 are correlated (Fig. 3) and strongly depend on density [76, 41, 77, 37, 52],  
361 and porosity [36] (see also sec. 4). As a consequence, a simplified model of  
362 cortical bone elastic properties with a limited number of parameters [78, 79]  
363 could be used in order to reduce the number of unknowns when solving  
364 the QUS inverse problem. Such an approach was implemented by Bochud  
365 et al. [69] where cortical bone was modeled as a pore network of variable  
366 porosity embedded in a matrix with fixed elastic properties [40, 80] (an  
367 implementation of the model is available online [81]; the model predictions  
368 are plotted against ex vivo elasticity measurements in Fig. 6).

## 369 **4. Measuring material properties as potential biomarkers of bone** 370 **health**

371 Managing bone health often starts by assessing the risk of fracture of  
372 an individual. This depends on many factors related to the risk of an in-  
373 dividual to fall, and to the ability of a bone to resist a low trauma. The  
374 latter depends both on bone size and geometry, and material properties. In  
375 this section, we briefly review the relationships between, on the one hand,  
376 material properties that may be derived in vivo from QUS measurements

377 and, on the other hand, strength, fracture risk factors, and quality of the  
378 extracellular matrix.

#### 379 *4.1. Bone resistance*

380 As mentioned in the introduction, one potential advantage of ultrasound  
381 over X-ray approaches is to assess material properties beyond the mere quan-  
382 tity of bone reflected in BMD measured with an X-ray based technique.

383 Bone resistance to fracture is typically characterized by strength (i.e.,  
384 ultimate stress before rupture) and toughness (i.e., resistance to crack prop-  
385 agation) [82]. It is yet unclear to which extent ultrasound, probing bone  
386 at very small strains in a linear regime, may yield information on bone  
387 resistance.

388 Correlations have been reported between bone resistance and elastic  
389 properties as for engineering and natural materials in general [83]. Indeed,  
390 post-yield and elastic properties are all determined by the biochemical com-  
391 position and the microstructure of bone. It is thus expected that elasticity  
392 and BWVs reflect material resistance to some extent. Pooling results of com-  
393 pression testing of children and adult bone, Öhman et al. [84] found a high  
394 correlation between yield stress and Young's modulus ( $R^2=0.88$ ). Weaker  
395 correlations have been found in studies considering only specimens from  
396 adult donors ( $R^2=0.25$  in three-point bending tests [85] ;  $R^2=0.53$  and  $0.56$   
397 in tension and compression tests, respectively [41]). Further studies should  
398 elucidate more precisely how much of bone material resistance (strength or  
399 toughness) can be learned from the measurement of elastic properties and  
400 BWVs.

#### 401 *4.2. Elasticity and bulk wave velocities reflect porosity and matrix properties*

402 Porosity, a fracture risk factor [15], is an important determinant of stiff-  
403 ness variations [86, 87]. Several authors have reported correlations between  
404 porosity and elastic moduli, although the range of correlation coefficients  
405 is quite large. For example, Mirzaali et al. [42] found  $R^2=0.08$  (Young's  
406 modulus) and  $R^2=0.47$  (shear modulus), Granke et al. [36] and Cai et al.  
407 [88] found  $R^2$  in the range 0.70-0.84 for all shear and longitudinal stiffness  
408 coefficients. Relatively large relative variations of stiffness in the porosity  
409 range [2.9-26.9%] were reported [36]: 58%, 34%, 48%, and 59% for  $C_{11}$ ,  $C_{33}$ ,  
410  $C_{44}$ , and  $C_{66}$ , respectively (Fig. 6). Overall, as porosity increases,  $C_{11}$  (lon-  
411 gitudinal elasticity transverse to Haversian canals) decreases more compared  
412 to  $C_{33}$  (longitudinal elasticity in the direction of Haversian canals). This is  
413 consistent with results of theoretical studies [89, 79, 40].

414 Data suggest that porosity is also a strong determinant of BWVs. In  
 415 axial direction, porosity was found to explain about 30% of BWV variation  
 416 [47, 48]. In radial direction it was found to explains about 50% of BWV  
 417 variations [45].

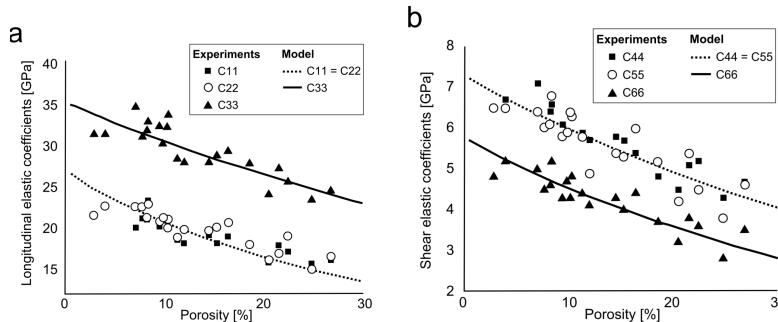


Figure 6: Reproduced from [36]. (a) Longitudinal and (b) shear mesoscopic elastic coefficients versus porosity in 21 cortical bone samples from the femur. The model based on continuum mechanics laws (solid and dotted lines), assuming fixed matrix properties and variable porosity, predicts the trend of variation of elasticity.

418 There is few data suggesting that variations of material properties of  
 419 the matrix may be reflected in QUS signals in human bones [90]. There is,  
 420 however, ex vivo data on prepared specimens pointing at an effect of matrix  
 421 properties variations on mesoscale elasticity. For instance, Rho et al. [91]  
 422 found that variations of the mesoscale axial Young's modulus ( $R^2=0.49$ )  
 423 correlated to the variations of the matrix elasticity (probed with nanoinden-  
 424 tation). Granke et al.[36] found that mesoscale elasticity was correlated with  
 425 matrix acoustical impedance (a proxy for stiffness) probed with acoustic mi-  
 426 croscopy ( $R^2 < 0.25$ ). In another study, variations of matrix impedance has  
 427 been found to explain as much as 52% of axial BWV [47]. Eneh et al. [92]  
 428 showed, with simulations performed on a limited number of samples, that  
 429 the correlation of BWV in the radial direction with porosity may be lost  
 430 due to inter-individual variations of matrix properties.

431 The main determinant of matrix stiffness variations is commonly thought  
 432 to be the mineral content. This is well evidenced considering a large variety  
 433 of bone samples taken from different species [86], and theoretical calcula-  
 434 tions predict that a change of 10% of mineral volume fraction leads to a  
 435 change of typically more than 20% of matrix elastic coefficients [93, 94, 78].  
 436 In a recent study on femoral bone specimens from 19 elderly donors, Cai  
 437 [88] found that more than 50% of mesoscale elasticity variations were asso-  
 438 ciated to variations of mineral content. Collagen fibers mechanical quality



439 and organizational patterns have also been proposed as possible determi-  
440 nants of mesoscopic properties. As far as we are aware, there is no data  
441 for human bone showing an effect of a pathological alteration of collagen on  
442 mesoscale elastic properties. However, artificial degradation of the collagen  
443 with chemical treatments is known to alter elastic properties [95].

444 From a mechanical standpoint, mesoscale cortical bone material proper-  
445 ties such as density, elasticity, or BWVs are fully determined by the proper-  
446 ties of the pore network and of the matrix. Whether or not a change of these  
447 properties is reflected at the mesoscale in a given dataset critically depends  
448 on the range of variations of the properties at the different scales. The data  
449 reported above was obtained from the tissues of donors with no documented  
450 medical history, hence the conclusions drawn from these studies only per-  
451 tain to this type of population and cannot be extrapolated to groups of  
452 subjects carrying specific bone diseases. To conclude, for these bones from  
453 non-targeted populations, the available data suggest that a large part of  
454 the elasticity and BWVs variations is explained by the variation of porosity.  
455 This is consistent with the prediction of theoretical models which assume  
456 that the matrix properties have limited inter-individual variations and that  
457 porosity varies in a relatively large interval [78, 80] (sec. 3.2.2). Variations  
458 of the properties of the matrix (mineral content, impedance, elasticity) also  
459 impact mesoscale elastic properties and BWVs, however, only limited data is  
460 available. Some pathologies involving a low mineral content or a weak align-  
461 ment of collagen fibers are expected to strongly affect mesoscale properties  
462 through modifications of both the porosity and the matrix. This calls for  
463 more studies designed to investigate the variations of BWVs and elasticity  
464 in different targeted populations.

#### 465 *4.3. Biomarkers of material heterogeneity*

466 Aging may be associated to an increase of the heterogeneity of the distri-  
467 bution and size of the pores in the cortical bone layer, resulting in a gradient  
468 of porosity: high porosity close to the marrow and relatively low porosity  
469 close to the external surface of the bone [8] . In terms of mechanics of  
470 materials, this raises the question of the existence of a representative vol-  
471 ume element of cortical bone material[28]. If the local variations of porosity  
472 are too strong, the cortical bone material can not be evaluated per se and  
473 the cortex needs to be considered as a structure. In case of a mild hetero-  
474 geneity of porosity, it may be relevant to model the cortex material as a  
475 heterogeneous field of material properties. This issue has in part been theo-  
476 retically addressed in an axial transmission QUS configuration [96, 97] but  
477 has not been implemented in clinical practice as far as we know. Since the

478 heterogeneity of material properties within the cortex is expectedly associ-  
479 ated to a reduced mechanical competence, it could be interesting to develop  
480 ultrasound biomarkers reflecting heterogeneity.

## 481 **5. Conclusion**

482 QUS technologies to measure cortical bone thickness, a proven biomarker  
483 of bone health, are available and used in vivo. Improvements of these tech-  
484 nologies and disruptive technologies are expected to be available in a near  
485 future, which will achieve a coupled assessment of cortical thickness and  
486 material properties. One motivation is to estimate intracortical porosity,  
487 a quantity hardly directly measurable in vivo. Assessing porosity with ul-  
488 trasound would be a significant progress because porosity is a recognized  
489 fracture risk factor and because it is a fingerprint of the remodeling activ-  
490 ity. One route to infer porosity is to use empirical relationships, or material  
491 models, relating quantities measured with QUS and porosity. Other routes  
492 are currently being explored such as imaging blood perfusion using ultra-  
493 sound contrast agent [98] and measuring ultrasonic attenuation assuming  
494 it has a strong relationship with pore properties [99].

495 Probing the quality of the mineralized collagen matrix in vivo with ul-  
496 trasound is a far-reaching goal. It may be a reasonable objective in targeted  
497 pathologies providing that alterations of porosity and matrix properties are  
498 well documented ex vivo. Such documentation of acoustical properties in  
499 bone tissue with different pathologies is a keystone of the future development  
500 of bone QUS methods.

## 501 **Acknowledgment**

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