



HAL
open science

Quantitative Ultrasound Assessment of Cortical Bone Properties Beyond Bone Mineral Density

Q. Grimal, P. Laugier

► **To cite this version:**

Q. Grimal, P. Laugier. Quantitative Ultrasound Assessment of Cortical Bone Properties Beyond Bone Mineral Density. Innovation and Research in BioMedical engineering, 2019, 40 (1), pp.16-24. 10.1016/j.irbm.2018.10.006 . hal-02328244

HAL Id: hal-02328244

<https://hal.sorbonne-universite.fr/hal-02328244v1>

Submitted on 23 Oct 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

3 Q. Grimal^a, P. Laugier^a

4 ^a*Sorbonne Université, INSERM, CNRS, Laboratoire d'Imagerie Biomédicale, LIB,*
5 *F-75006 Paris, France*

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

26 **Graphical abstract**

27 **Highlights**

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

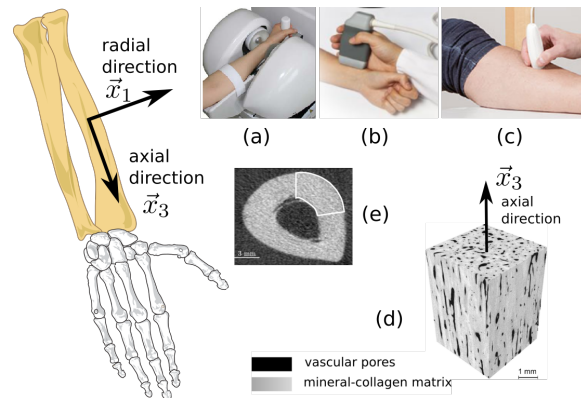


Figure 1: *

[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**

38 Grimal Q, Laugier P. Quantitative ultrasound assessment of cortical bone
 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 μm . 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

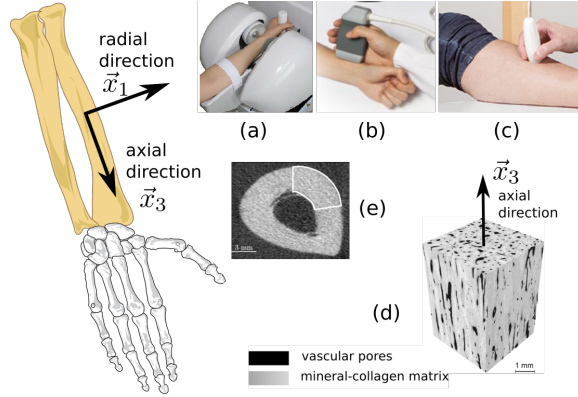


Figure 2: Bone anatomy and QUS measurement configurations. (a) Measurement in bone radial direction with a through transmission approach (courtesy of OYO Electric CO., LTD., Japan); (b) Measurement in bone axial direction with bidirectional axial transmission to measure guided waves (courtesy of AZALEE, 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 σ_i and ϵ_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 ρ 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 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 (± 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 (± 486) and 3994 m/s (± 178). Grondin et al.
211 [47], combining measurements in several quadrants of the femur of 4 donors
212 found 3976 m/s (± 72) for axial BWV. Mathieu et al. [48] investigated the
213 radial variation of axial BWV in 11 femurs and found 3586 m/s (± 255). In

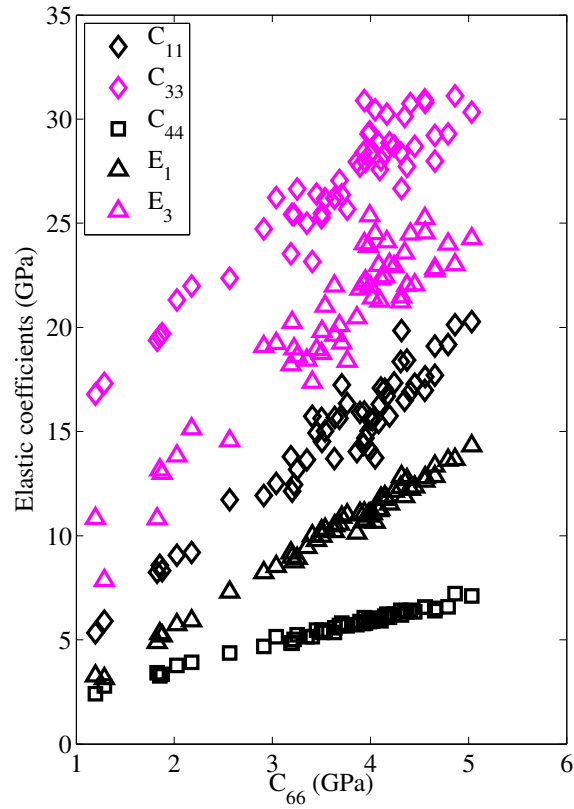


Figure 3: This figure, reproduced from [37], illustrates the ranges of variations of elastic coefficients (ex vivo measurements). Stiffness and engineering coefficients of 55 cortical bone specimens from the tibia, are plotted as a function of C_{66} to illustrate the interdependency of the different 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 ± 1.5 standard deviation) 3311 m/s (± 307) in men and
 217 3359 m/s (± 297) in women.

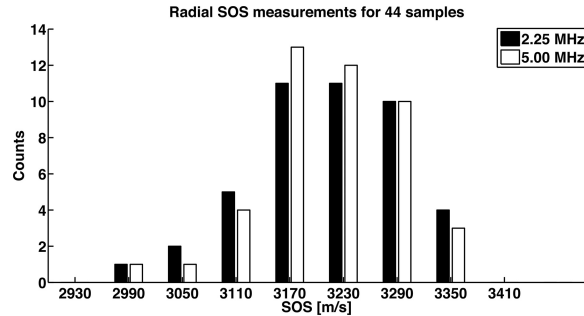


Figure 4: Reproduced from [45]. Histogram (numbers represent the center of bins that are 60 m/s in width) of the average values of radial bulk wave velocity (denoted SOS for 'speed of sound' in the figure) in 44 cortical bone samples from the femur diaphysis. The black and white bars represent radial 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⁻³, 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.

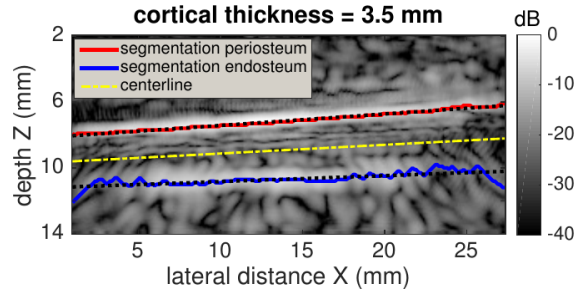


Figure 5: Reproduced from [73]. Ultrasound image of the cortical layer of a radius in vivo. Red and blue lines correspond to the periosteum and endosteum. Straight lines (dotted black line) approximate the interfaces. The cortical thickness, defined as the mean distance between these lines is found to 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].

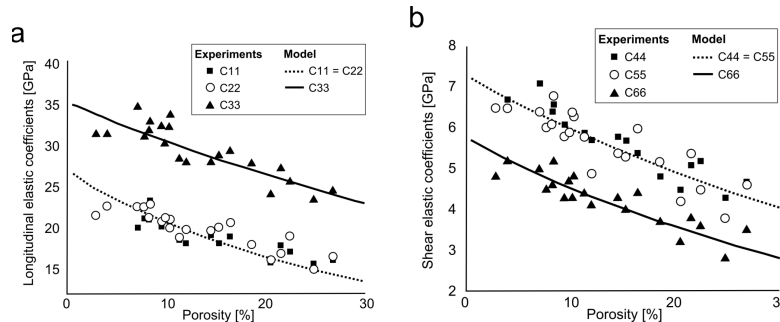


Figure 6: Reproduced from [36]. (a) Longitudinal and (b) shear mesoscopic elastic coefficients versus porosity in 21 cortical bone samples from the femur. The model based on continuum mechanics laws (solid and dotted lines), assuming fixed matrix properties and variable porosity, predicts the trend of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

- 502 [1] C Cooper and F Ferrari. IOF Compendium of Osteoporosis. Technical
503 report, International Osteoporosis Foundation, 2017.
- 504 [2] E S Siris, Y T Chen, T A Abbott, E Barrett-Connor, P D Miller,
505 L E Wehren, and M L Berger. Bone mineral density thresholds for
506 pharmacological intervention to prevent fractures. *Archives of Internal
507 Medicine*, 164(10):1108–1112, 2004.
- 508 [3] Karine Briot, Simon Paternotte, Sami Kolta, Richard Eastell, Di-
509 eter Felsenberg, David M. Reid, Claus C. Glüer, and Christian Roux.
510 FRAX®: Prediction of major osteoporotic fractures in women from
511 the general population: The OPUS study. *PLoS ONE*, 8(12), 2013.

- 512 [4] A. M. Parfitt. Misconceptions (2): Turnover is always higher in cancel-
513 lous than in cortical bone. *Bone*, 30(6):807–809, 2002.
- 514 [5] Paul M Mayhew, C David Thomas, John G Clement, Nigel Loveridge,
515 Thomas J Beck, William Bonfield, Chris J Burgoyne, and Jonathan
516 Reeve. Relation between age, femoral neck cortical stability, and hip
517 fracture risk. *The Lancet*, 366(9480):129–135, 2005.
- 518 [6] Gerold Holzer, Gobert von Skrbensky, Lukas A Holzer, and Wolfgang
519 Pichl. Hip fractures and the contribution of cortical versus trabecular
520 bone to femoral neck strength. *J Bone Miner Res*, 24(3):468–474, mar
521 2009.
- 522 [7] P Augat, H Reeb, and L E Claes. Prediction of fracture load at different
523 skeletal sites by geometric properties of the cortical shell. *J Bone Miner
524 Res*, 11(9):1356–1363, 1996.
- 525 [8] R M D Zebaze, A Ghasem-Zadeh, A Bohte, S Iuliano-Burns, M Mirams,
526 R I Price, E J Mackie, and E Seeman. Intracortical remodelling and
527 porosity in the distal radius and post-mortem femurs of women: a cross-
528 sectional study. *Lancet*, 375(9727):1729–1736, 2010.
- 529 [9] Patrick Ammann, Isabelle Badoud, Sébastien Barraud, Romain Dayer,
530 and René Rizzoli. Strontium ranelate treatment improves trabecu-
531 lar and cortical intrinsic bone tissue quality, a determinant of bone
532 strength. *Journal of Bone and Mineral Research*, 22(9):1419–1425,
533 2007.
- 534 [10] Yohann Bala, Baptiste Depalle, Delphine Farlay, Thierry Douillard,
535 Sylvain Meille, Helene Follet, Roland Chapurlat, J??r??me Chevalier,
536 and Georges Boivin. Bone micromechanical properties are compromised
537 during long-term alendronate therapy independently of mineralization.
538 *Journal of Bone and Mineral Research*, 27(4):825–834, 2012.
- 539 [11] Laurianne Imbert, Jean-Charles Aurégan, Kélig Pernelle, and Thierry
540 Hoc. Mechanical and mineral properties of osteogenesis imperfecta hu-
541 man bones at the tissue level. *Bone*, 65:18–24, 2014.
- 542 [12] Jirko Kühnisch, Jong Seto, Claudia Lange, Susanne Schrof, Sabine
543 Stumpp, Karolina Kobus, Julia Grohmann, Nadine Kossler, Peter
544 Varga, Monika Osswald, Denise Emmerich, Sigrid Tinschert, Falk
545 Thielemann, Georg Duda, Wenke Seifert, Thaqif El Khassawna,
546 David A. Stevenson, Florent Elefteriou, Uwe Kornak, Kay Raum, Peter

- 547 Fratzl, Stefan Mundlos, and Mateusz Kolanczyk. Multiscale, converg-
548 ing defects of macro-porosity, microstructure and matrix mineralization
549 impact long bone fragility in NF1. *PLoS ONE*, 9(1):1–12, 2014.
- 550 [13] V Bousson, A Meunier, Bergot C., E Vicaut, M A Rocha, M H Morais,
551 A M Laval-Jeantet, and J D Laredo. Distribution of intracortical poros-
552 ity in human midfemoral cortex by age and gender. *Journal of Bone*
553 *and Mineral Research*, 16:1308–1317, 2001.
- 554 [14] L. A. Ahmed, R. Shigdel, R. M. Joakimsen, O. P. Eldevik, E. F. Erik-
555 sen, A. Ghasem-Zadeh, Y. Bala, R. Zebaze, E. Seeman, and Bjørnerem.
556 Measurement of cortical porosity of the proximal femur improves iden-
557 tification of women with nonvertebral fragility fractures. *Osteoporosis*
558 *International*, 26(8):2137–2146, 2015.
- 559 [15] Yohann Bala, Roger Zebaze, and Ego Seeman. Role of cortical bone in
560 bone fragility. *Current Opinion in Rheumatology*, 27(4):406–413, 2015.
- 561 [16] Roger Zebaze, Cesar Libanati, Michael R. McClung, José R. Zanchetta,
562 David L. Kendler, Arne Høiseth, Andrea Wang, Ali Ghasem-Zadeh, and
563 Ego Seeman. Denosumab Reduces Cortical Porosity of the Proximal
564 Femoral Shaft in Postmenopausal Women With Osteoporosis. *Journal*
565 *of Bone and Mineral Research*, 31(10):1827–1834, 2016.
- 566 [17] Kyle K. Nishiyama, Heather M. Macdonald, Helen R. Buie, David A.
567 Hanley, and Steven K. Boyd. Postmenopausal women with osteopenia
568 have higher cortical porosity and thinner cortices at the distal radius
569 and tibia than women with normal aBMD: An in vivo HR-pQCT study.
570 *Journal of Bone and Mineral Research*, 25(4):882–890, 2010.
- 571 [18] Piet Geusens, Roland Chapurlat, Georg Schett, Ali Ghasem-Zadeh, Ego
572 Seeman, Joost De Jong, and Joop Van Den Bergh. High-resolution in
573 vivo imaging of bone and joints: A window to microarchitecture, may
574 2014.
- 575 [19] Adolfo Diez-Perez, Roberto Güerri, Xavier Nogues, Enric Cáceres,
576 Maria Jesus Peñ, Leonardo Mellibovsky, Connor Randal, Daniel
577 Bridges, James C. Weaver, Alexander Proctor, Davis Brimer, Kurt J.
578 Koester, Robert O. Ritchie, and Paul K. Hansma. Microindentation for
579 in vivo measurement of bone tissue mechanical properties in humans.
580 *Journal of Bone and Mineral Research*, 25(8):1877–1885, 2010.

- 581 [20] P Laugier. Instrumentation for in vivo ultrasonic characterization
582 of bone strength. *IEEE Trans Ultrason Ferroelectr Freq Control*,
583 55(6):1179–1196, 2008.
- 584 [21] Kay Raum, Quentin Grimal, Peter Varga, Reinhard Barkmann,
585 Claus C Glüer, and Pascal Laugier. Ultrasound to assess bone quality.
586 *Curr Osteoporos Rep*, 12(2):154–162, 2014.
- 587 [22] E. V. McCloskey, J. A. Kanis, A. Odén, N. C. Harvey, D. Bauer,
588 J. González-Macias, D. Hans, S. Kaptoge, M. A. Krieg, T. Kwok,
589 F. Marin, A. Moayyeri, E. Orwoll, C. Glüer, and H. Johansson. Pre-
590 dictive ability of heel quantitative ultrasound for incident fractures: an
591 individual-level meta-analysis. *Osteoporosis International*, 26(7):1979–
592 1987, 2015.
- 593 [23] Sergio Casciaro, Francesco Conversano, Paola Pisani, and Maurizio Mu-
594 ratore. New perspectives in echographic diagnosis of osteoporosis on hip
595 and spine. *Clinical Cases in Mineral and Bone Metabolism*, 12(2):142–
596 150, 2015.
- 597 [24] J. P. Karjalainen, O. Riekkinen, and H. Kröger. Pulse-echo ultra-
598 sound method for detection of post-menopausal women with osteo-
599 porotic BMD. *Osteoporosis International*, pages 1–7, 2018.
- 600 [25] Claus C. Glüer. A new quality of bone ultrasound research. *IEEE*
601 *Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*,
602 55(7):1524–1528, 2008.
- 603 [26] Jarne Karjalainen, Ossi Riekkinen, Juha Töyräs, Heikki Kröger, and
604 Jukka Jurvelin. Ultrasonic assessment of cortical bone thickness in
605 vitro and in vivo. *IEEE Transactions on Ultrasonics, Ferroelectrics,*
606 *and Frequency Control*, 55(10):2191–2197, 2008.
- 607 [27] Petro Moilanen. Ultrasonic guided waves in bone. *IEEE Transactions*
608 *on Ultrasonics, Ferroelectrics, and Frequency Control*, 55(6):1277–1286,
609 2008.
- 610 [28] Quentin Grimal, Kay Raum, Alf Gerisch, and Pascal Laugier. A de-
611 termination of the minimum sizes of representative volume elements
612 for the prediction of cortical bone elastic properties. *Biomech Model*
613 *Mechanobiol*, 10(6):925–937, 2011.

- 614 [29] D. M.L. Cooper, C. E. Kawalilak, K. Harrison, B. D. Johnston, and
615 J. D. Johnston. Cortical Bone Porosity: What Is It, Why Is It Im-
616 portant, and How Can We Detect It? *Current Osteoporosis Reports*,
617 14(5):187–198, 2016.
- 618 [30] M Petrtyl, J Hert, and P Fiala. Spatial organization of the haversian
619 bone in man. *Journal of Biomechanics*, 29(2):161–167, 1996.
- 620 [31] C D Thomas, S A Feik, and J G Clement. Increase in pore area, and not
621 pore density, is the main determinant in the development of porosity in
622 human cortical bone. *J Anat.*, 209(2):219–30., 2006.
- 623 [32] M K H Malo, D Rohrbach, H Isaksson, J Töyräs, J S Jurvelin, I S
624 Tamminen, H Kröger, and K Raum. Longitudinal elastic properties
625 and porosity of cortical bone tissue vary with age in human proximal
626 femur. *Bone*, 53(2):451–458, jan 2013.
- 627 [33] Egon Perilli, Yohann Bala, Roger Zebaze, Karen J Reynolds, and Ego
628 Seeman. Regional Heterogeneity in the Configuration of the Intracortical
629 Canals of the Femoral Shaft. *Calcif Tissue Int*, 97(4):327–335, oct
630 2015.
- 631 [34] S C Cowin. *Bone mechanics handbook*, volume 1. CRC Press, Boca
632 Raton, FL, second edition, 2001.
- 633 [35] David J Rudy, Justin M Deuerling, Alejandro A Espinoza Orías, and
634 Ryan K Roeder. Anatomic variation in the elastic inhomogeneity and
635 anisotropy of human femoral cortical bone tissue is consistent across
636 multiple donors. *J Biomech*, 44(9):1817–1820, 2011.
- 637 [36] Mathilde Granke, Quentin Grimal, Amena Saïed, Pierre Nauleau,
638 Françoise Peyrin, and Pascal Laugier. Change in porosity is the major
639 determinant of the variation of cortical bone elasticity at the millimeter
640 scale in aged women. *Bone*, 49(5):1020–1026, 2011.
- 641 [37] Simon Bernard, Joannes Schneider, Peter Varga, Pascal Laugier, Kay
642 Raum, and Quentin Grimal. Elasticity-density and viscoelasticity-
643 density relationships at the tibia mid-diaphysis assessed from resonant
644 ultrasound spectroscopy measurements. *Biomech Model Mechanobiol*,
645 15(1):97–109, 2016.
- 646 [38] Q Grimal, K Raum, A Gerisch, and P Laugier. Derivation of the meso-
647 scopic elasticity tensor of cortical bone from quantitative impedance

- 648 images at the micron scale. *Computer Methods in Biomechanics and*
649 *Biomedical Engineering*, 11(2):147–157, 2008.
- 650 [39] Andrew P Baumann, Justin M Deuerling, David J Rudy, Glen L Niebur,
651 and Ryan K Roeder. The relative influence of apatite crystal orien-
652 tations and intracortical porosity on the elastic anisotropy of human
653 cortical bone. *J Biomech*, 45(16):2743–2749, nov 2012.
- 654 [40] William J Parnell, M B Vu, Q Grimal, and S Naili. Analytical methods
655 to determine the effective mesoscopic and macroscopic elastic properties
656 of cortical bone. *Biomech Model Mechanobiol*, 11:883–901, nov 2012.
- 657 [41] L Duchemin, V Bousson, C Raossanaly, C Bergot, J D Laredo, W Skalli,
658 and D Mitton. Prediction of mechanical properties of cortical bone
659 by quantitative computed tomography. *Med Eng Phys*, 30(3):321–328,
660 2008.
- 661 [42] Mohammad J. Mirzaali, J. Jakob Schwiedrzik, Suwanwadee Thaiwichai,
662 James P. Best, Johann Michler, Philippe K. Zysset, and Uwe Wol-
663 fram. Mechanical properties of cortical bone and their relationships
664 with age, gender, composition and microindentation properties in the
665 elderly. *Bone*, 93:196–211, 2016.
- 666 [43] P Roschger, E P Paschalis, P Fratzl, and K Klaushofer. Bone mineral-
667 ization density distribution in health and disease. *Bone*, 42(3):456–466,
668 mar 2008.
- 669 [44] R B Ashman, S C Cowin, W C van Buskirk, and J C Rice. A continuous
670 wave technique for the measurement of the elastic properties of cortical
671 bone. *Journal of Biomechanics*, 17(5):349–361, 1984.
- 672 [45] C. T.M. Eneh, M. K.H. Malo, J. P. Karjalainen, J. Liukkonen,
673 J. Töyräs, and J. S. Jurvelin. Effect of porosity, tissue density, and
674 mechanical properties on radial sound speed in human cortical bone.
675 *Medical Physics*, 43(5):2030–2039, 2016.
- 676 [46] Emmanuelle Lefèvre, Philippe Lasaygues, Cécile Baron, Cédric Payan,
677 Franck Launay, Hélène Follet, and Martine Pithioux. Analyzing the
678 anisotropic Hooke’s law for children’s cortical bone.
679 *J Mech Behav Biomed Mater*, 49:370–377, sep 2015.
- 680 [47] Julien Grondin, Quentin Grimal, Kazufumi Yamamoto, Mami Mat-
681 sukawa, Amena Saïed, and Pascal Laugier. Relative contributions of

- 682 porosity and mineralized matrix properties to the bulk axial ultrasonic
683 wave velocity in human cortical bone. *Ultrasonics*, 52(4):467–471, 2012.
- 684 [48] Vincent Mathieu, Christine Chappard, Romain Vayron, Adrien Michel,
685 and Guillaume Haïat. Radial anatomic variation of ultrasonic ve-
686 locity in human cortical bone. *Ultrasound in Medicine and Biology*,
687 39(11):2185–2193, 2013.
- 688 [49] M Greenfield, J Duncan Craven, Alan Huddleston, Mary Kehrer, David
689 Wishko, and Richard Stern. Measurement of the Velocity of Ultrasound
690 in Human Cortical. *radiation physics*, 138:701–710, 1981.
- 691 [50] Adam D G Baxter-Jones, Robert A Faulkner, Mark R Forwood,
692 Robert L Mirwald, and Donald A Bailey. Bone mineral accrual from
693 8 to 30 years of age: an estimation of peak bone mass. *J Bone Miner
694 Res*, 26(8):1729–1739, 2011.
- 695 [51] S Bernard, Q Grimal, and P Laugier. Accurate measurement of cortical
696 bone elasticity tensor with resonant ultrasound spectroscopy. *Journal
697 of the Mechanical Behavior of Biomedical Materials*, 18:12–19, 2013.
- 698 [52] L. Peralta, X. Cai, P. Laugier, and Q. Grimal. A critical assessment
699 of the in-vitro measurement of cortical bone stiffness with ultrasound.
700 *Ultrasonics*, 80:119–126, 2017.
- 701 [53] P Laugier and G Haïat, editors. *Bone Quantitative ultrasound*.
702 Springer, New York, 2010.
- 703 [54] E Camus, M Talmant, G Berger, and P Laugier. Analysis of the axial
704 transmission technique for the assessment of skeletal status. *Journal of
705 the Acoustical Society of America*, 108:3058–3065, 2000.
- 706 [55] Quentin Vallet, Nicolas Bochud, Christine Chappard, Pascal Laugier,
707 and Jean-Gabriel Minonzio. In vivo characterization of cortical bone us-
708 ing guided waves measured by axial transmission. *IEEE Trans Ultrason
709 Ferroelectr Freq Control*, 2016.
- 710 [56] K A Wear. Autocorrelation and cepstral methods for measurement of
711 tibial cortical thickness. *Ieee Transactions on Ultrasonics Ferroelectrics
712 and Frequency Control*, 50(6):655–660, 2003.
- 713 [57] H. Sai, G. Iguchi, T. Tobimatsu, K. Takahashi, T. Otani, K. Horii,
714 I. Mano, I. Nagai, H. Iio, T. Fujita, K. Yoh, and H. Baba. Novel ultra-
715 sonic bone densitometry based on two longitudinal waves: Significant

- 716 correlation with pQCT measurement values and age-related changes
717 in trabecular bone density, cortical thickness, and elastic modulus of
718 trabecular bone in a normal Japanese po. *Osteoporosis International*,
719 21(10):1781–1790, 2010.
- 720 [58] Alexey Tatarinov, Armen Sarvazyan, Gisela Beller, and Dieter Felsen-
721 berg. Comparative Examination of Human Proximal Tibiae In Vitro
722 by Ultrasonic Guided Waves and pQCT. *Ultrasound in Medicine and*
723 *Biology*, 37(11):1791–1801, 2011.
- 724 [59] Petro Moilanen, Patrick H.F. Nicholson, Vantte Kilappa, Sulin Cheng,
725 and Jussi Timonen. Assessment of the cortical bone thickness using
726 ultrasonic guided waves: Modelling and in vitro study. *Ultrasound in*
727 *Medicine & Biology*, 33(2):254–262, feb 2007.
- 728 [60] J G Minonzio, M Talmant, and P Laugier. Guided wave phase veloc-
729 ity measurement using multi-emitter and multi-receiver arrays in the
730 axial transmission configuration. *Journal of the Acoustical Society of*
731 *America*, 127(5):2913–2919, 2010.
- 732 [61] T. Mishima, K. Motoyama, Y. Imanishi, K. Hamamoto, Y. Nagata,
733 S. Yamada, N. Kuriyama, Y. Watanabe, M. Emoto, and M. Inaba.
734 Decreased cortical thickness, as estimated by a newly developed ultra-
735 sound device, as a risk for vertebral fracture in type 2 diabetes mellitus
736 patients with eGFR of less than 60 mL/min/1.73 m². *Osteoporosis*
737 *International*, 26(1):229–236, 2015.
- 738 [62] J. P. Karjalainen, O. Riekkinen, J. Töyräs, M. Hakulinen, H. Kröger,
739 T. Rikkinen, K. Salovaara, and J. S. Jurvelin. Multi-site bone ultra-
740 sound measurements in elderly women with and without previous hip
741 fractures. *Osteoporosis International*, 23(4):1287–1295, 2012.
- 742 [63] J. T. Schousboe, O. Riekkinen, and J. Karjalainen. Prediction of hip
743 osteoporosis by DXA using a novel pulse-echo ultrasound device. *Os-*
744 *teoporosis International*, 28(1):85–93, 2017.
- 745 [64] Janina M. Patsch, Andrew J. Burghardt, Samuel P. Yap, Thomas
746 Baum, Ann V. Schwartz, Gabby B. Joseph, and Thomas M. Link. In-
747 creased cortical porosity in type 2 diabetic postmenopausal women with
748 fragility fractures. *Journal of Bone and Mineral Research*, 28(2):313–
749 324, 2013.

- 750 [65] R Longo, Q Grimal, P Laugier, S Vanlanduit, and P Guillaume. Simul-
751 taneous Determination of Acoustic Velocity and Density of a Cortical
752 Bone Slab: Ultrasonic Model-Based Approach. *Ieee Transactions on*
753 *Ultrasonics Ferroelectrics and Frequency Control*, 57(2):496–500, 2010.
- 754 [66] Matthieu Loosvelt and Philippe Lasaygues. A Wavelet-Based Process-
755 ing method for simultaneously determining ultrasonic velocity and ma-
756 terial thickness. *Ultrasonics*, 51(3):325–339, 2011.
- 757 [67] Yuriy Tasinkevych, Jerzy Podhajecki, Katarzyna Falińska, and Jerzy
758 Litniewski. Simultaneous estimation of cortical bone thickness and
759 acoustic wave velocity using a multivariable optimization approach:
760 Bone phantom and in-vitro study. *Ultrasonics*, 65:105–112, 2016.
- 761 [68] Josquin Foiret, Jean-Gabriel Minonzio, Christine Chappard, Maryline
762 Talmant, and Pascal Laugier. Combined estimation of thickness and
763 velocities using ultrasound guided waves: a pioneering study on in vitro
764 cortical bone samples. *IEEE Trans Ultrason Ferroelectr Freq Control*,
765 61(9):1478–1488, sep 2014.
- 766 [69] N. Bochud, Q. Vallet, Y. Bala, H. Follet, J. G. Minonzio, and
767 P. Laugier. Genetic algorithms-based inversion of multimode guided
768 waves for cortical bone characterization. *Physics in Medicine and Bi-*
769 *ology*, 61(19):6953–6974, 2016.
- 770 [70] J.-G. Minonzio, N. Bochud, Q. Vallet, Y. Bala, D. Ramiandrisoa,
771 H. Follet, D. Mitton, and P. Laugier. Bone cortical thickness and poros-
772 ity assessment using ultrasonic guided waves: an ex vivo validation
773 study. *Bone*, submitted, 2018.
- 774 [71] Valeria Beltrame, Roberto Stramare, Nicola Rebellato, Federico An-
775 gelini, Anna Chiara Frigo, and Leopoldo Rubaltelli. Sonographic eval-
776 uation of bone fractures: A reliable alternative in clinical practice?
777 *Clinical Imaging*, 36(3):203–208, 2012.
- 778 [72] R. Zheng, L.H. Le, M.D. Sacchi, and E. Lou. Imaging internal structure
779 of long bones using wave scattering theory. *Ultrasound in Medicine and*
780 *Biology*, 41(11), 2015.
- 781 [73] G. Renaud, P. Kruizinga, D. Cassereau, and P. Laugier. In vivo ultra-
782 sound imaging of the bone cortex. *Phys Med Biol*, 63(12):125010, Jun
783 2018.

- 784 [74] P Lasaygues. Assessing the cortical thickness of long bone shafts in
785 children, using two-dimensional ultrasonic diffraction tomography. *Ul-*
786 *trasound in Medicine and Biology*, 32(8):1215–1227, 2006.
- 787 [75] Simon Bernard, Vadim Monteiller, Dimitri Komatitsch, and Philippe
788 Lasaygues. Ultrasonic computed tomography based on full-waveform
789 inversion for bone quantitative imaging. *Physics in Medicine and Biol-*
790 *ogy*, 62(17):7011–7035, 2017.
- 791 [76] J Y Rho, M C Hobatho, and R B Ashman. Relations of mechanical
792 properties to density and CT numbers in human bone. *Med Eng Phys*,
793 17(5):347–55., 1995.
- 794 [77] A A Espinoza Orías, J M Deuerling, M D Landrigan, J E Renaud, and
795 R K Roeder. Anatomic variation in the elastic anisotropy of cortical
796 bone tissue in the human femur. *J Mech Behav Biomed Mater*, 2(3):255–
797 263, 2009.
- 798 [78] Quentin Grimal, Guillermo Rus, William J Parnell, and Pascal Laugier.
799 A two-parameter model of the effective elastic tensor for cortical bone.
800 *J Biomech*, 44(8):1621–1625, 2011.
- 801 [79] Ch Hellmich and F J Ulm. can the diverse elastic properties of trabec-
802 ular and cortical bone be attributed to only a few tissue-independent
803 phase properties and their interactions? *Biomechanics and Modeling*
804 *in Mechanobiology*, 2:219–238, 2004.
- 805 [80] Mathilde Granke, Quentin Grimal, William J Parnell, Kay Raum, Alf
806 Gerisch, Françoise Peyrin, Amena Saïed, and Pascal Laugier. To what
807 extent can cortical bone millimeter scale elasticity be predicted by a
808 two phase composite model with variable porosity? *Acta Biomater*,
809 12:207–215, oct 2015.
- 810 [81] William Grimal, Quentin, Parnell. BonHom: program for homogeniza-
811 tion.
- 812 [82] Elizabeth A Zimmermann, Björn Busse, and Robert O Ritchie. The
813 fracture mechanics of human bone: influence of disease and treatment.
814 *Bonekey Rep*, 4:743, 2015.
- 815 [83] M F Ashby and D R H Jones. *Engineering materials 1*. Elsevier,
816 Amsterdam, 3rd edition, 2005.

- 817 [84] Caroline Öhman, Massimiliano Baleani, Carla Pani, Fulvia Taddei,
818 Marco Alberghini, Marco Viceconti, and Marco Manfrini. Compressive
819 behaviour of child and adult cortical bone. *Bone*, 49(4):769–776,
820 oct 2011.
- 821 [85] Q Grimal, S Hauptert, D Mitton, L Vastel, and P Laugier. Assessment
822 of cortical bone elasticity and strength: Mechanical testing and ultra-
823 sound provide complementary data. *Medical Engineering & Physics*,
824 31(9):1140–1147, 2009.
- 825 [86] J D Currey. The effect of porosity and mineral content on the Young’s
826 modulus of elasticity of compact bone. *J Biomech*, 21(2):131–139, 1988.
- 827 [87] M B Schaffler and D B Burr. Stiffness of compact bone: effects of
828 porosity and density. *J Biomech*, 21(1):13–16, 1988.
- 829 [88] Xiran Cai. *Multiscale investigation of the elastic properties of human*
830 *cortical bone measured by resonant ultrasound spectroscopy*. PhD thesis,
831 Sorbonne Université, 2018.
- 832 [89] C Baron, M Talmant, and P Laugier. Effect of porosity on effective
833 diagonal stiffness coefficients (cii) and elastic anisotropy of cortical bone
834 at 1 MHz: a finite-difference time domain study. *J Acoust Soc Am*,
835 122(3):1810, 2007.
- 836 [90] K Raum, I Leguerney, F Chandelier, E Bossy, M Talmant, A Saied,
837 F Peyrin, and P Laugier. Bone microstructure and elastic tissue prop-
838 erties are reflected in QUS axial transmission measurements. *Ultrasound*
839 *in Medicine and Biology*, 31(9):1225–35., 2005.
- 840 [91] J Y Rho, P Zioupos, J D Currey, and G M Pharr. Microstructural elas-
841 ticity and regional heterogeneity in human femoral bone of various ages
842 examined by nano-indentation. *Journal of Biomechanics*, 35(2):189–
843 98., 2002.
- 844 [92] Chibuzor T. M. Eneh, Jukka Liukkonen, Markus K. H. Malo, Jukka S.
845 Jurvelin, and Juha Töyräs. Inter-individual changes in cortical bone
846 three-dimensional microstructure and elastic coefficient have opposite
847 effects on radial sound speed. *The Journal of the Acoustical Society of*
848 *America*, 138(6):3491–3499, 2015.
- 849 [93] Christian Hellmich, Jean-Francois Barthelemy, and Luc Dormieux.
850 Mineral-collagen interactions in elasticity of bone ultrastructure - a

- 851 continuum micromechanics approach. *European Journal of Mechanics*
852 - *A/Solids*, 23(5):783–810, 2004.
- 853 [94] J M Deuerling, W M Yue, A A E Orias, and R K Roeder. Specimen-
854 specific multi-scale model for the anisotropic elastic constants of human
855 cortical bone. *Journal of Biomechanics*, 42(13):2061–2067, 2009.
- 856 [95] S S Mehta, O K Oz, and P P Antich. Bone elasticity and ultrasound
857 velocity are affected by subtle changes in the organic matrix. *J Bone*
858 *Miner Res*, 13(1):114–21., 1998.
- 859 [96] G Haiat, S Naili, Q Grimal, M Talmant, C Desceliers, and C Soize.
860 Influence of a gradient of material properties on ultrasonic wave prop-
861 agation in cortical bone: Application to axial transmission. *Journal of*
862 *the Acoustical Society of America*, 125(6):4043–4052, 2009.
- 863 [97] Cécile Baron. Using the Gradient of Human Cortical Bone Properties
864 to Determine Age-Related Bone Changes Via Ultrasonic Guided Waves.
865 *Ultrasound in Medicine and Biology*, 38(6):972–981, 2012.
- 866 [98] J. Du, G. Iori, and K. Raum. Imaging of cortical pores using ultrasound
867 contrast agents: Phantom and ex vivo studies. In *IEEE International*
868 *Ultrasonics Symposium, IUS*, 2017.
- 869 [99] Omid Yousefian, R. D. White, Yasamin Karbalaieisadegh, H. T. Banks,
870 and Marie Muller. The effect of pore size and density on ultrasonic
871 attenuation in porous structures with mono-disperse random pore dis-
872 tribution: A two-dimensional in-silico study. *JOURNAL OF THE*
873 *ACOUSTICAL SOCIETY OF AMERICA*, 144(2):709–719, AUG 2018.