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# In vivo pulse-echo measurement of apparent broadband attenuation and Q factor in cortical bone: A preliminary study

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# Abstract

Quantitative UltraSound (QUS) methods have been introduced to assess cortical bone health at the radius and tibia through the assessment of Cortical Thickness (Ct.Th), Cortical Porosity (Ct.Po) and bulk wave velocities. Ultrasonic attenuation is another QUS parameter which is not currently used. We assess the feasibility of *in vivo* measurement of ultrasonic attenuation in cortical bone with a broadband transducer with 3.5 MHz-center frequency. Echoes from the periosteal and endosteal interfaces were fitted with Gaussian pulses using sparse signal processing. Then, the slope of the Broadband Ultrasonic Attenuation (Ct.nBUA) in cortical bone and quality factor  $Q_{11}^{-1}$ were calculated with a parametric approach based on the center-frequency shift. Five human subjects were measured at the one-third distal radius with pulse-echo ultrasound, and reference data was obtained with high-resolution X-ray peripheral computed tomography (Ct.Th and Cortical volumetric Bone Mineral Density, Ct.vBMD). Ct.Th was used in the calculation of Ct.nBUA while  $Q_{11}^{-1}$  is obtained solely from ultrasound data. The values of Ct.nBUA

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 $(6.7\pm2.2 \text{ dB.MHz.}^{-1}.\text{cm}^{-1})$  and  $Q_{11}^{-1}$  (8.6±3.1 %) were consistent with the literature data and were correlated to Ct.vBMD ( $R^2 = 0.92$ , p < 0.01,  $RMSE = 0.56 \text{ dB.MHz}^{-1}.\text{cm}^{-1}$ , and  $R^2 = 0.93$ , p < 0.01, RMSE= 0.76%). This preliminary study suggests that the attenuation of an ultrasound signal propagating in cortical bone can be measured *in vivo* at the one-third distal radius and that it provides an information on bone quality as attenuation values. It remains to ascertain that Ct.nBUA and  $Q_{11}^{-1}$  measured here exactly reflect the true (intrinsic) ultrasonic attenuation in cortical bone. Measurement of attenuation may be considered useful for assessing bone health combined with the measurement of cortical thickness, porosity and bulk wave velocities in multimodal cortical bone QUS methods.

*Keywords:* cortical bone, broadband ultrasonic attenuation, Quantitative Ultrasound, *in vivo* measurement, Orthogonal Matching Pursuit, sparse reconstruction, Q factor

# <sup>1</sup> Introduction

Osteoporosis fracture risk is currently assessed using Dual energy X-2 ray Absorptiometry (DXA) in order to assess areal Bone Mineral Density 3 (aBMD). However, DXA has strong limitations, in particular it lacks sensitivity (Briot et al., 2013; Siris, 2004) and is not appropriate to monitor 5 cortical bone (Choksi et al., 2018). Cortical bone, the dense tissue that 6 forms the outer shells of the bones, represents about 80% of the human 7 skeleton mass and plays an important role in the skeletal mechanical stability (Holzer et al., 2009; Zebaze et al., 2010; Bala et al., 2014). Aging 9 and bone pathologies are associated with cortical thinning (Nishiyama et al., 10 2010) and weakening of the bone material mechanical quality reflected in 11 an increase of Cortical Porosity (Ct.Po) (Kral et al., 2017) or a decrease of 12 Cortical volumetric Bone Mineral Density (Ct.vBMD (CT.vBMD) (Ostertag 13 et al., 2016; Paranhos Neto et al., 2019). 14

Several quantitative ultrasound (QUS) approaches have been introduced 15 to assess cortical bone health at the radius and tibia. Some aim at assessing 16 Cortical Thickness (Ct.Th) assuming a nominal value of ultrasound veloc-17 ity using pulse-echo (Karjalainen et al., 2008), axial transmission (Moilanen, 18 2008), or through transmission measurements (Sai et al., 2010). Other ap-19 proaches are designed for a combined estimation of Ct. Th and Ct. Po or bulk 20 wave velocities using axial transmission measurements of several guided wave 21 modes (Foiret et al., 2014; Minonzio et al., 2019) or adaptative pulse-echo 22 imaging with a transducer array (Renaud et al., 2018, 2020). Ultrasonic at-23 tenuation is another QUS parameter which has been exploited for several 24 decades in soft tissues (Mamou and Oelze, 2013) and trabecular bone (Lang-25 ton and Njeh, 2008); however, until now, it has received little consideration 26 in cortical bone QUS. 27

Ex vivo studies on cuboid specimens have established that ultrasonic at-28 tenuation of bulk waves in cortical bone is related to mass density (Bernard 29 et al., 2015) and to Ct.vBMD (Sasso et al., 2008). Also, simulations have sug-30 gested that the scattering of ultrasound by the cavities of the pore network 31 is one important mechanism of attenuation (Yousefian et al., 2018, 2021; Iori 32 et al., 2020). It follows that, in addition to ultrasonic velocities measured 33 with QUS approaches (Grimal and Laugier, 2019), attenuation could be in-34 dicative of the mechanical quality of cortical bone as it is related to Ct.Po 35 and Ct.vBMD. 36

There has been a few attempts to measure attenuation in *ex vivo* bone

specimens. Zheng et al. (2007) measured in pulse echo mode a bovine femur 38 specimen and estimated the slope of the frequency-dependent attenuation co-39 efficient (also referred to as "spectral ratio method") to estimate the so-called 40 Cortical normalized Broadband Ultrasonic Attenuation (Ct.nBUA). They 41 later used a parametric approach introduced by Kuc et al. (1976) which re-42 lated attenuation to the shift of the center frequency (also referred to as "peak 43 frequency method") (Zheng et al., 2009). Dencks et al. (2008) also used this 44 parametric approach and measured nBUA in proximal femurs in through-45 transmission. However, these values of nBUA can hardly be interpreted in 46 terms of bulk cortical bone material properties because ultrasound propa-47 gated along a complex path through both cortical and trabecular bone. As 48 far as we know, in vivo measurements of attenuation in cortical bone have 49 not yet been reported. 50

The aim of this paper was to assess the feasibility of *in vivo* measurement 51 of attenuation in cortical bone. We have conducted a preliminary study on 52 the radius of five human subjects. Ultrasound echoes stemming from the 53 normal-incidence reflection on the outer (periosteal) and inner (endosteal) 54 cortical bone interfaces were recorded and processed with Orthogonal Match-55 ing Pursuit (OMP) to retrieve the time delay, the temporal echo width and 56 the frequency shift of the center frequency from which Ct.nBUA and the 57 quality factor Q were calculated with a parametric approach (Kuc et al., 58 1976). The quality factor is introduced as a quantity related to the dissipa-59 tion of energy which can be measured without the need of the knowledge of 60 the bulk wave velocity. Ultrasound parameters Ct.nBUA and Q were com-61 pared to reference values of Ct.vBMD of each subject which were obtained 62 with High-Resolution X-ray peripheral Quantitative Computed Tomography 63 (HR-pQCT). The results are of interest for the development of future multi-64 modal cortical bone QUS approaches estimating bone structural (thickness) 65 and material (porosity, velocities, attenuation) properties for the evaluation 66 of bone health. 67

### 68 1. Method

#### 69 1.1. Extraction of echoes

The signal received in the pulse-echo ultrasound measurement is modeled as a sum of two Gaussian pulses  $s_i(t)$ , or Gabor functions, i.e., the product of a Gaussian function with a complex sinusoid (Demirli and Saniie, 2001)

$$y(t) = \sum_{i=1}^{2} s_i(t) + n(t) = \sum_{i=1}^{2} A_i \exp\left[-\frac{(t-t_i)^2}{2\sigma_{t_i}^2}\right] \cos\left[2\pi f_i(t-t_i)\right] + n(t), \quad (1)$$

<sup>73</sup> where  $\sigma_{t_i}$  is the standard deviation of the temporal Gaussian function,  $f_i$  is <sup>74</sup> the central frequency,  $t_i$  is the group delay and  $A_i$  is the amplitude of *i*-th <sup>75</sup> echo. The error between the model and the measured signal, including noise, <sup>76</sup> is n(t). The first and second echoes correspond to the reflections on the outer <sup>77</sup> (periosteal) and inner (endosteal) bone surfaces, respectively.

<sup>78</sup> For further use, we write the temporal Fourier transform of one echo as

$$S_i(f) = \frac{A_i}{\sqrt{2\pi\sigma_{fi}}} \exp[-\frac{(f-f_i)^2}{2\sigma_{fi}^2}] \exp[-j2\pi f t_i],$$
(2)

<sup>79</sup> where the standard deviation of the Gaussian function  $\sigma_{f_i}$  satisfies  $2\pi\sigma_{f_i} = 1/\sigma_{t_i}$ . The -6dB frequency bandwidth, or full width at half maximum, is <sup>81</sup> related to  $\sigma_{f_i}$ , and is equal to  $2\sqrt{2\ln(2)}\sigma_{f_i} \approx 2.35\sigma_{f_i}$ .

The echoes are isolated using a sparse signal processing method in the time domain which provides the quantities  $\sigma_{t_i}$ ,  $f_i$ ,  $t_i$ , and  $A_i$  (i = 1, 2). The method is detailed in Appendix ; shortly, the signal model, given by (1), discretized in time can be represented as

$$\mathbf{y} = \mathbf{D}\mathbf{x} + \mathbf{n},\tag{3}$$

where y and n are  $N_t \times 1$  vectors corresponding to the sampling of y(t) and 86 n(t) at  $N_t$  discrete time points, respectively. Likewise, **x** is a  $N_m \times 1$  vector 87 collecting the  $N_m$  relative amplitudes of the echoes. In a sparse point of view, 88 only a few elements of this vector are non zero. Finally, **D** is a  $N_t \times N_m$  ma-89 trix corresponding the so-called dictionary. Each column  $\mathbf{d}(t; \sigma_{t_m}, f_m, t_m)$ , 90 with  $m = 1 \cdots M$ , of **D** is one of the M Gabor functions discretized at 91  $N_t$  time points, defined by the set of parameters  $(\sigma_{t_m}, f_m, t_m)$ . For a given 92 measurement y(t), the problem amounts to determine the two non-zero com-93 ponents of  $\mathbf{x}$ , which indices yield the set of parameters corresponding to the 94 two echoes. This is done by sparse reconstruction with Orthogonal Matching 95 Pursuit (OMP) (Tropp and Gilbert, 2007). The details of the construction of 96 the dictionary and of the implementation of OMP can be found in Appendix. 97

#### 98 1.2. Measurement of attenuation: Theory

The cortical bone layer is modeled locally as a plate of thickness Ct.Th. 99 We assume that the temporal signals can be decomposed into monochromatic 100 plane waves propagating in bone at normal incidence on the plate surfaces. 101 The complex wavenumber is denoted  $(k + i\alpha)$ , where  $\alpha$  is the imaginary part 102 and is assumed to present a linear attenuation with frequency in cortical 103 bone, i.e.,  $\alpha = \beta f$  (Minonzio et al., 2011). This linear approximation, or 104 first order Taylor expansion, is valid around a central frequency  $f_0$  as long as 105 the frequency deviation  $\Delta f$  is narrow, i.e.,  $\Delta f/f_0 \ll 1$ , even if the attenua-106 tion variation for larger frequency is not linear (Szabo, 1995; Yousefian et al., 107 2021). Note that the real part k of the wavenumber is assumed to be fre-108 quency independent within the considered bandwidth. With this plane wave 109 model, the modulus of the ratio of the spectra of the two echoes (from the pe-110 riosteal and endosteal surfaces) is proportional to  $\exp(-\beta f 2Ct.Th)$  (Zheng 111 et al., 2009). Note that the ultrasound signal does not need to be corrected 112 for the overlying soft tissues, as we are studying the ratio between endosteal 113 and periosteal echoes. Both echoes are indeed equally affected by the prop-114 agation within the soft tissue layer. Thus, the ratio only depends on the 115 propagation inside the cortical bone layer. 116

<sup>117</sup> Following Kuc (Kuc et al., 1976), the attenuation coefficient  $\beta$  can be <sup>118</sup> estimated from pulse-echo measurements with a parametric approach from <sup>119</sup> the shift of the center frequency of the Gaussian pulse. Assuming that the <sup>120</sup> central frequency variation  $\Delta f = f_1 - f_2$  is small compared to the central <sup>121</sup> frequency (i.e.,  $\sigma_f$  remains unchanged), the coefficient  $\beta$  writes (Kuc et al., <sup>122</sup> 1976; Narayana and Ophir, 1983)

$$\beta = \frac{1}{2Ct.Th} \frac{\Delta f}{\sigma_f^2},\tag{4}$$

with the frequency in MHz and distance in mm,  $\beta$  is in Np.mm<sup>-1</sup>.MHz<sup>-1</sup>. This parametric estimation is well adapted in both transmission (Kuc et al., 1976) and reflection (Kuc, 1984) and has been successfully applied to bone on *ex vivo* specimens in both configurations (Dencks et al., 2008; Zheng et al., 2007, 2009). Finally, the cortical broadband ultrasound attenuation in dB.cm<sup>-1</sup>.MHz<sup>-1</sup>, is obtained as

$$Ct.nBUA = 10 \frac{20}{\ln(10)} \beta \approx 86.9\beta.$$
(5)

<sup>129</sup> The above equations indicate that the experimental determination of <sup>130</sup> nBUA or  $\beta$  requires the knowledge of Ct.Th. This can be obtained from <sup>131</sup> the X-ray computed tomography scan of the bone, or, alternatively, from <sup>132</sup> ultrasound signals as

$$Ct.Th = v_{11}\frac{\Delta t}{2},\tag{6}$$

where  $\Delta t = t_2 - t_1$ , providing the longitudinal bulk wave velocity  $v_{11}$  (in mm. $\mu s^{-1}$ ) is known. The index "11" refers to the radial bone direction commonly denoted direction 1 in previous studies (Foiret et al., 2014; Bernard et al., 2015). In a first approach, a nominal value of  $v_{11}$  may be assumed, i.e., the velocity is supposed to be known and identical for all subjects (Karjalainen et al., 2008; Grimal and Laugier, 2019). Thus, the  $\beta$  coefficient may be rewritten without reference to Ct.Th, using equations (4) and (6), as

$$\beta = 2 \frac{\pi}{v_{11}} \frac{\sigma_t}{\Delta t} \frac{\Delta f}{\sigma_f}.$$
(7)

The quality factor Q is a dimensionless parameter, classically used to 140 describe the resonance of a resonator, usually defined by the ratio between the 141 central frequency and the frequency bandwidth. High Q values correspond 142 to low attenuation. It is possible to define a quality factor related bulk 143 wave velocity  $v_{11}$  as  $Q_{11}^{-1} = \frac{\Im(C_{11})}{\Re(C_{11})}$  (Bernard et al., 2015), where  $C_{11}$  is the 144 complex elastic coefficient related to  $v_{11}$ . Interestingly, as we show below, 145  $Q_{11}^{-1}$  does not require the knowledge of the bulk wave velocity. In case of weak attenuation, i.e.,  $Q_{11}^{-1} \ll 1$  or  $\alpha \ll k$ , which is usually satisfied in 146 147 cortical bone at low frequency, i.e., less than a few MHz, (Bernard et al., 148 2015), the quality factors writes 149

$$Q_{11}^{-1} \approx \frac{2\alpha}{k} \approx \frac{\beta v_{11}}{\pi}.$$
(8)

<sup>150</sup> Which can advantageously be rewritten

$$Q_{11}^{-1} \approx \frac{1}{\pi \sigma_f^2} \frac{\Delta f}{\Delta t},\tag{9}$$

which expression does not depend on the bulk wave velocity  $v_{11}$  but only on the parameters  $\Delta t$ ,  $\Delta f$  and  $\sigma_f$  which can be extracted from the measured <sup>153</sup> signals. Thus, evaluating  $Q_{11}^{-1}$  to measure attenuation could be an advantage <sup>154</sup> as this does not require the knowledge of the bulk wave velocity.

#### 155 1.3. In vivo ultrasound measurements

This study has been approved by the ethical committee of the Committees 156 for the protection of persons Sud-Méditerranée. A written informed consent 157 was provided by the five healthy subjects (24-38 years old) recruited in this 158 study. The ultrasound measurements were approximately performed in the 159 one-third distal extremity of the left radius. Precisely, a mark with a pen was 160 done on the upper medial part of the forearm at 7 cm from the radial styloid 161 and the transducer was positioned on this mark. This position exactly cor-162 responded to the center of the region of interest scanned with HR-pQCT. A 163 3.5 MHz-center frequency mono element transducer (Olympus V384, 25-mm 164 diameter, - 6dB bandwidth of 2.03MHz, Webster, TX 77598, USA) was used. 165 The transducer was connected to a wave pulse/receiver (Olympus 5077PR 166 SQUARE, Waltham, MA 02453, USA) and an oscilloscope (PicoScope 5000 167 Series, Picotechnology, Cambridgeshire, United Kingdom) for data acquisi-168 The sampling frequency was equal to 125 MHz. Ultrasound echoes tion. 169 stemming from the reflection on the outer (periosteal) and inner (endosteal) 170 cortical bone interfaces were recorded. The waveform of the received signal 171 was displayed on the computer screen in real time. The operator ensured 172 a correct positioning of the probe (perpendicular to interfaces) by slightly 173 moving the probe so as to minimize the time delay between echoes. When 174 a satisfactory position was achieved, the operator started the acquisition of 175 30 consecutive signals. Note that the ultrasound signal does not need to be 176 corrected for the overlying soft tissues, as we are studying the ratio between 177 endosteal and periosteal echoes. 178

In order to illustrate the validity of the linear frequency dependence of 179 the attenuation coefficient, a typical example of *in vivo* pulse echo measure-180 ment is shown in Figure 1. The two separated echoes can be observed on 181 Figure 1(a), while the two associated spectra  $S_1(f)$  and  $S_2(f)$  are shown in 182 Figure 1(b). Those spectra were obtained by the temporal Fourier trans-183 forms of segments  $s_1(t)$  and  $s_2(t)$ , indicated with thick lines, corresponding 184 to 1.2  $\mu$ s from each side of the envelop maxima (Karjalainen et al., 2008). 185 Finally, on Figure 1(c), one can observe that the variation of the spectrum 186 ratio  $\ln(|S_2(f)/S_1(f)|)$  is in agreement with the slope  $\Delta f/\sigma_f^2$  of the linear 187 approximation (Kuc et al., 1976). Note that the spectral ratio method is 188

based on the slope evaluation, while the peak frequency method is based onKuc's formula.



Figure 1: An example of received echoes (for subject number 3) and illustration of the linear frequency dependence of the attenuation coefficient : (a) complete temporal ultrasound signal and retained segments  $s_1(t)$  and  $s_2(t)$ ; (b) frequency spectrum of the two echoes and (c) spectrum ratio  $ln(|S_2(f)/S_1(f)|)$  compared with the slope  $\Delta f/\sigma_f^2$  obtained with Kuc's formula . The parameters  $t_{1,2}$ ,  $f_{1,2}$  and  $\sigma_t$  obtained with OMP in this study are indicated on the figures.

Processing of the signal with OMP yields the parameters  $(\sigma_{f_1}, f_1, t_1)$  and 191  $(\sigma_{f_2}, f_2, t_2)$  of the echoes which were used to calculate Ct.nBUA (eq. 5) us-192 ing the cortical thickness value obtained from HR-pQCT (see section 1.4) 193 (eq. 4) and  $Q_{11}^{-1}$  (eq. 9). The extraction of the parameters  $(\sigma_{t_1}, f_1, t_1)$  and 194  $(\sigma_{t_2}, f_2, t_2)$  is illustrated on Figure 1 using the same signal as for figure 1. 195 It can be observed in Figure 2(b) that the retained parameters (best model 196 number m) are associated with the two maxima, for all m, of the scalar prod-197  $||uct| < s(t)|\mathbf{d}(t; \sigma_{t_m}, f_m, t_m)|| >$ between the dictionary and the signal. The 198 maximum of this scalar product can be interpreted as the maximum quality 199 of the signal fit, as the dictionary vectors **d** are normalized. Accordingly, for 200 each subject, we retained the 10 (out of 30) measurements with the highest 201 values in order to remove the poorest measurements corresponding e.g., to a 202 poor alignment of the probe with the bone surface. The final values of nBUA 203 and  $Q_{11}^{-1}$ , and their errors, were obtained using the mean and the standard 204 deviation calculated on the 10 retained measurements. 205



Figure 2: Principle of the evaluation of the parameters  $(\sigma_{t_m}, f_m, t_m)$  of the Gabor functions matching the two echoes using OMP. Original signal y(t) compared with the two reconstructed echoes  $s_1(t)$  (blue) and  $s_2(t)$  (black) (a) associated with dictionary indices m corresponding to the two largest values of the scalar product between the signal and the dictionary (b). (c): zoom around the first maximum.

# 206 1.4. HR-pQCT

The left radius of each subject was scanned with high-resolution X-ray 207 peripheral computed tomography (HR-pQCT, XtremeCT, Scanco Medical, 208 Brüttisellen, Switzerland) using the standard manufacturer in vivo acqui-209 sition parameters (60 kVp, 1000 mA, 100 ms integration time, voxel size 210  $82 \ \mu m$ ). The measurements were approximately performed at the one-third 211 distal radius site. To ensure that HR-pQCT imaging is site-matched with 212 ultrasound measurement, we used an initial large view image allowing to 213 center the scanning windows at 7 cm from the radial styloid corresponding 214 to the ultrasound measurement point. The acquired volume corresponded to 215 9.02 mm along the bone axis (110 cross-sectional slices). The central slice 216 is illustrated in Figure 3 for each subject. The region of interest (ROI), 217 site-matched with the ultrasound measurement site, is highlighted. Meth-218 ods used to process the CT data have been previously described in detail 219 (Laib et al., 1998; Boutroy et al., 2005; MacNeil and Boyd, 2007; Ostertag 220 et al., 2016). Briefly, cortical limits were determined using a threshold-based 221 algorithm. The threshold used to discriminate cortical bone was set to one 222

third of the apparent cortical bone density value (Dcort). Cortical thickness was calculated for each slice as the mean distance between the periosteal and endosteal contours. Finally, the mean and standard deviation of all slice cortical thickness was retained for each subject. Volumetric bone mineral density of the cortical bone in the ROI (Ct.vBMD) was obtained directly from Dcort. The mean and standard deviation of all slice Dcort was retained for each subject.



Figure 3: A representative cross-sectional HR-pQCT slice of the radius for each subject. The region of interest corresponding the ultrasound measurement site is highlighted

# 230 1.5. Data analysis

The relationships between ultrasound parameters and reference parameters obtained with HR-pQCT were assessed using linear correlations. We <sup>233</sup> report Pearson's correlation coefficient and linear regression equations.

#### 234 **Results**

The mean and standard deviation, calculated over the ten retained measurements, of the estimated parameters  $\Delta t$ ,  $\Delta f$ ,  $\sigma_f$  for each subject are reported in Table 1. The next last column corresponds to  $Q_{11}^{-1}$  obtained combining previous parameters using equation (9). Finally, values of Ct.Th,  $\Delta f$  and  $\sigma_f$  were used to compute Ct.nBUA according to equations (4) and (5) (last column of Table 1). HR-pQCT parameters Ct.Th and Ct.vBMD are reported in Table 2.

High correlations were observed between  $Q_{11}^{-1}$  and Ct.vBMD, obtained 242 by HR-pQCT ( $R^2 = 0.93$ , p < 0.01, RMSE= 0.76%, Fig. 4) and between 243 Ct.nBUA and Ct.vBMD ( $R^2 = 0.92, p < 0.01, RMSE = 0.56 dB.MHz^{-1}.cm^{-1}$ 244 Fig. 5). The linear regression equation was  $Ct.nBUA = -34.1 \times Ct.vBMD +$ 245 45.6, where Ct.nBUA is expressed in  $dB.MHz^{-1}.cm^{-1}$  and Ct.vBMD in 246 g.cm<sup>-3</sup>. Likewise, the second linear regression equation was  $Q_{11}^{-1} = -49.2 \times \text{Ct.vBMD} + 64.9$ , where  $Q_{11}^{-1}$  is expressed in % and Ct.vBMD in g.cm<sup>-3</sup>. The 247 248 corresponding longitudinal bulk wave velocities  $v_{11}$ , ranging from 3.2 to 3.9 249  $mm.\mu s^{-1}$ , are given in Table 3 for comparison with other studies. 250



Figure 4: Correlation between quality factor  $Q_{11}^{-1}$  obtained by pulse echo and Ct.vBMD obtained by HR-pQCT.



Figure 5: Correlation between Ct.nBUA and Ct.vBMD.

### 251 Discussion

This work considered pulse-echo measurements to measure the attenu-252 ation of signals from ultrasonic waves propagating in cortical bone at the 253 radius *in vivo*. The two echoes stemming from normal-incidence reflections 254 on the periosteal and endosteal bone surfaces were modeled as the sum of 255 two elementary waveforms (Gabor functions), and the parameters of these 256 waveforms (time delay, central frequency and frequency bandwidth) were re-257 covered using sparse signal processing (OMP). Attenuation was assessed in 258 two ways: (1) as Ct.nBUA with a parametric method using OMP parame-259 ters combined with Ct.Th from HR-pQCT; and (2) as a quality factor  $Q_{11}^{-1}$ 260 calculated from OMP parameters only. 261

The values of Ct.nBUA ( $6.7\pm2.2$  dB.MHz.<sup>-1</sup>.cm<sup>-1</sup>) are in the range of the attenuation values reported in the literature on bovine and human femur (Table 4). To which extent Ct.nBUA and  $Q_{11}^{-1}$  reflect the true (intrinsic) ultrasonic attenuation in cortical bone remains to be investigated. Such quantity can only be evaluated *ex vivo* using dedicated experimental conditions in order to minimize the effect of diffraction and other losses unrelated to attenuation within the tissue.

We found that Ct.nBUA was strongly correlated to volumetric bone mineral density (Ct.vBMD) measured from X-ray attenuation ( $R^2 = 0.92$ , Fig.5).

This finding is in line with the ex vivo results of Sasso et al. (Sasso et al., 271 2008) who reported a correlation between Ct.nBUA and Ct.vBMD in bovine 272 bone measured ex vivo  $(R^2 = 0.57, p < 10^{-5}, RMSE=1.6)$ . These au-273 thors also reported the linear fit equation between Ct.nBUA and Ct.vBMD 274  $(Ct.nBUA = -25.2 \times Ct.vBMD + 40.6)$  which can be compared to our re-275 sult (Ct.nBUA =  $-34.1 \times \text{Ct.vBMD} + 45.6$ ). The differences between these 276 equations may in part be due to the Ct.vBMD range which was different in 277 the two studies: [1.15-1.65] g.cm<sup>-3</sup> in (Sasso et al., 2008) compared [1.05-278 1.22] g.cm<sup>-3</sup> in the present study. 279

Quality factor  $Q_{11}^{-1}$  (Table 1) values associated to the propagation of a 280 longitudinal wave can be compared to shear mode quality factor  $Q_{44}^{-1}$  mea-281 sured from the first resonance peak (falling in the range [100–300 kHz]) of a 282 cuboid bone specimen (Bernard et al., 2015). In the latter study, the aver-283 age  $Q_{44}^{-1}$  was 3.5% to be compared to a mean value of 8.6% in the present 284 study. These values compare well although the comparison should be made 285 with caution because (i)  $Q_{44}^{-1}$  was obtained at a much lower frequency (one 286 order of magnitude); (ii) the polarization is different and a larger attenuation 287 is expected for shear waves; (iii) the collection of samples used in (Bernard 288 et al., 2015) includes low density (high porosity) samples which may not be 289 representative of the bone of healthy volunteers in the present study. 290

Ct.nBUA was calculated from measured ultrasound parameters and a 291 value of Ct.Th obtained from the HR-pQCT image of each subject. If only 292 ultrasound data is available, the quality factor  $Q_{11}^{-1}$  can be calculated as it 293 does not depend on the bulk wave velocity (Eq. 9). Our results suggest that 294  $Q_{11}^{-1}$  could be of clinical interest as it is correlated with Ct.vBMD ( $R^2 = 0.92$ , 295 Fig.4). Furthermore, Fan et al. (2021) have shown that the shear wave quality 296 factor is correlated to porosity  $(R^2=0.53)$ , and it is reasonable to infer that 297  $Q_{11}^{-1}$  measured in this study is also related to porosity. 298

Signal parameters were estimated in the ultrasound signal with OMP. 299 which has several advantages. The segmentation of the two echoes in the 300 time domain was performed automatically in a robust manner, which can 301 be an advantage in case of overlapping of echoes (which can occur for thin 302 cortices). Also, because the Gabor function offers a reliable parametrization 303 of the echoes, the calculation of Fourier domain parameters is done avoiding 304 a Fourier transform of the signal which can be polluted by the choice of the 305 time window for time segmentation. 306

The parametric method used to estimate attenuation relies on the measurement of  $\Delta f$ . In equation (7),  $\beta$  is written in terms of temporal and

frequency shifts divided by their associated standard deviations, leading to 309 normalized shifts or Z-scores. Using equations (8),  $Q_{11}^{-1}$  can also be written 310 in term of these ratios as  $\frac{\Delta f}{\sigma_f} = \frac{1}{2}Q_{11}^{-1}\frac{\Delta t}{\sigma_t}$ . As the ratio  $\Delta t/\sigma_t$  is of the order of 311 1 and  $Q_{11}^{-1}$  is small compared to 1, one can expect the ratio  $\Delta f/\sigma_f$  to be also 312 small compared to 1 in accordance with the weak attenuation hypothesis. 313 Thus, special attention should be paid to the evaluation of  $\Delta f$ . Indeed, it 314 can be observed in Table 1 that the largest relative uncertainties, up to 70%, 315 are obtained for the frequency  $\Delta f$  parameter, while the uncertainties on the 316 temporal  $\Delta t$  parameter are about a few percents. This observation should 317 be taken into account in order to propose a robust clinical measurement. 318

The calculation of Ct.nBUA requires the knowledge of cortical thickness Ct.Th, which was obtained from HR-pQCT in the present proof-of-concept study. Our method to measure attenuation could however be implemented together with other ultrasound sequences and signal processing providing speed of sound and cortical thickness as described in Renaud et al. (2018) or Nguyen Minh et al. (2020).

This study has a number of limitations. (1) Only 5 healthy subjects 325 were considered. The range of cortical bone properties (thickness, material 326 properties) may not be representative of the general population or subjects 327 with bone pathologies. (2) The endosteal interface of cortical bone of young 328 healthy subjects is known to be quasi-plane and regular, whereas it is likely 329 to be irregular and discontinuous for elderly subjects or patients with bone 330 diseases as a result of age- or disease-related bone deterioration and trabec-331 ularization (Zebaze et al., 2010). Such irregular interface may give rise to a 332 wave pattern more complex than the specular echo observed in the young sub-333 jects in the present study. Also, as the attenuation is expected to increase 334 with porosity, the signal from the endosteal interface in osteoporostic or old 335 patients should be weaker compared to the signals processed in this study. 336 The applicability of our method to assess aged or diseased bone remains to 337 be assessed. (3) Because the probe was handheld, some pulse echo acqui-338 sitions had to be discarded. We used a quality criterion provided by OMP 339 processing based on the value of the scalar product between the recorded 340 signal and the dictionary. This criterion is believed to be robust as it relies 341 on the expected shape of the echo waveform. Nevertheless, reproducibility of 342 the method should be assessed in future studies on a larger number of sub-343 jects. Moreover, all measurements have been carried out at the same central 344 frequency of 3.5 MHz. This frequency may need to be adapted for smaller or 345

larger thicknesses in order to remain with an endosteal echo clearly separated
and not too much attenuated. As attenuation in cortical bone may have a
nonlinear dependence on frequency(Yousefian et al., 2021), attenuation values obtained at different frequencies may not be directly compared with the
values obtained in the present study.

The results of this study suggest that ultrasonic quantities (Ct.nBUA and 351  $Q_{11}^{-1}$ ) related to attenuation in cortical bone can be measured in vivo at the 352 radius, which provide an information on bone quality as they were found to 353 be highly correlated to Ct.vBMD values. Indeed, Ct.vBMD is an established 354 biomarker of bone health related to bone porosity and mineralization (En-355 gelke, 2017). If these results are confirmed in studies with a larger number 356 and diversity of subjects, measurement of attenuation may be considered 357 useful for assessing bone health. This can be combined with the measure-358 ment of cortical thickness, porosity and bulk wave velocities in multimodal 350 cortical bone QUS evaluation methods. Future studies should investigate to 360 which extent Ct.nBUA and  $Q_{11}^{-1}$  measured with the method of this study 361 reflect the true (intrinsic) ultrasonic attenuation in cortical bone. Advanced 362 signal processing techniques such as neural network (Mohanty et al., 2019), 363 machine learning (Minonzio et al., 2020) or deep learning (Li et al., 2021) 364 will be investigated in order to improve the robustness of the approach. 365

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### 374 APPENDIX: Orthogonal Matching Pursuit

#### 375 Dictionary

To implement the sparse signal processing method, the first issue is to discretize the Gabor functions into an over-complete dictionary  $\mathbf{D}$ , where the columns of  $\mathbf{D}$  are built resorting to the Gabor functions basis

$$\mathbf{d}(t, \mathbf{\Theta}) = \zeta_{\mathbf{\Theta}} \exp[-s(t-\tau)^2] \exp[j2\pi f(t-\tau)]$$
(.1)

$$= [s, \tau, f] \tag{(.2)}$$

where  $\zeta_{\Theta}$  is a normalization parameter that ensures  $\|\mathbf{d}(\Theta, t)\|_2 = 1$   $(l_2$ -379 norm). To build a suitable elementary atom of  $\mathbf{D}$ , the columns use a dis-380 cretization of the different parameters that characterize each Gabor func-381 tion. The possible values of the set of parameters  $\Theta$  are sampled on M 382 discrete points. For this purpose, we define an a priori range for s,  $\tau$ , and 383 f, these ranges being subdivided into L, S and K regular intervals, respec-384 tively. Furthermore, each Gabor function is sampled at  $N_t$  discrete time 385 points  $\mathbf{t} = [t_1, t_2, \cdots, t_{N_t}]$ . The dimension of the over-complete dictionary is  $M = L \times S \times K$ , with  $M \gg N_t$ . The dictionary can be represented as 387

Θ

$$\mathbf{D} = \begin{bmatrix} d(t_1, \Theta_1) & d(t_1, \Theta_2) & \cdots & d(t_1, \Theta_M) \\ d(t_2, \Theta_1) & d(t_2, \Theta_2) & \cdots & d(t_2, \Theta_M) \\ \vdots & \vdots & \ddots & \vdots \\ d(t_{N_t}, \Theta_1) & d(t_{N_t}, \Theta_2) & \cdots & d(t_{N_t}, \Theta_M) \end{bmatrix}$$
(.3)

388 where

$$\Theta_m = [s_l, \tau_s, f_k], \\ l \in [1, L], s \in [1, S], k \in [1, K], m \in [1, M].$$

The ranges of variations of s,  $\tau$  and k are defined as follows. The range 389 of frequency f can be obtained from the bandwidth of the received signal, as 390 discussed in (Mor et al., 2010). Similarly, the range for the bandwidth factor 391 s can be deduced from the bandwidth of the emitted signal. The time delays 392  $\tau$  of the different echoes are searched around the peaks of the envelope of 393 the received signal. Overall, the selection of the parameter intervals is quite 394 flexible due to the robustness and efficiency of the OMP method. Using the 395 dictionary, the signal model (1) can be represented as 396

$$\mathbf{y} = \mathbf{D}\mathbf{x} + \mathbf{n} \tag{.4}$$

where  $\mathbf{y}$  and  $\mathbf{n}$  are the sampling of y(t) and n(t) at discrete time points respectively,  $\mathbf{x}$  is the amplitude vector corresponding to each column in  $\mathbf{D}$ . This dictionary can be interpreted as an extension of the classical Fourier transform. In the case of the temporal Fourier transform,  $\Theta$  is reduced to the frequency f and a element of the dictionary matrix writes as  $d(t, \Theta) = d(t, f) = exp(-j2\pi ft)$  and previous equation, i.e., the signal reconstruction, corresponds to the inverse Fourier transform. In case of the Gabor basis, the reconstruction is sparse, i.e., only a finite number of function are necessary for reconstruction, contrary to the Fourier basis for which the reconstruction is continuous.

We evaluated the numerical cost of the OMP algorithm. For a dictionary size varying from  $1000 \times 50000$  ( $N_t = 1000; L = 20, K = 10, S = 250$ ) to  $1000 \times 80000$  ( $N_t = 1000; L = 20, K = 10, S = 400$ ), the computation time ranges approximately between 0.2 and 0.7 s on a standard personal computer (Intel(R) Xeon(R) CPU E5-2620 v2 at 2.10GHz, 32Gbytes memory, Dell, USA).

# 413 Orthogonal Matching Pursuit with complex dictionary

The application considered in this paper is the reconstruction the echoes 414 from the periosteal and endosteal surfaces of the cortical bone. Accordingly, 415 we restrain our analysis to the two first echoes, thus we set P = 2 in (1). 416 As a consequence, we expect only 2 non-zero components of  $\mathbf{x}$ , which is 417 much smaller than its dimension (M). The determination of the two main 418 echoes requires only two iterations using sparsity constrained OMP. Since the 419 columns of the dictionary defined in (3) are complex-valued, the correspond-420 ing steps of the OMP have to be adapted. Each iteration step consists in 421 searching the best matching column with the residual from the previous iter-422 ation. In the case of a complex dictionary, the matching between a particular 423 complex column and the given signal r is (Lu and Michaels, 2008) 424

$$\langle \mathbf{r}, \mathbf{d}^H \rangle = \mathbf{d}^H \mathbf{r} = C e^{j\phi}$$
 (.5)

where **r** is the residual signal from last iteration, H denotes the complex conjugate transpose operator, C indicates the matching level and  $\phi$  the phase of the residual.

The best correlated column from the dictionary **D** corresponds to the largest value of C. The corresponding position index in vector **x** is denoted

$$i_{max} = \max_{i} \{ |\mathbf{D}(:,i)^H \mathbf{r}| \}, \tag{.6}$$

430 and the phase is given by

$$\phi = \text{angle}\{\mathbf{D}(:, i_{max})^H \mathbf{r}\}.$$
 (.7)

It should be noticed that the residual cannot be iterated directly, since it is defined as the linear combination of two real Gaussian pulses instead of complex-values Gabor functions as introduced in (.1). After computation of (.6) and (.7), The real Gaussian pulses  $\mathbf{D}_r(i_{max})$  are obtained using the relationship

$$\mathbf{D}_{r}(:, i_{max}) = \Re\{\mathbf{D}(:, i_{max})e^{-j\phi}\}.$$
(.8)

<sup>436</sup> The OMP processing is illustrated in Algorithm 1.

| Algorithm 1 Orthogonal Matching Pursuit algorithm  |  |  |  |  |
|--|--|--|--|--|
| <b>Input:</b> $\mathbf{y} \in \mathbb{R}^N$ , $\mathbf{D} \in \mathbb{C}^{N \times M}$ , target sparsity=2 |  |  |  |  |
| <b>Output:</b> sparse solution $\mathbf{x} \in \mathbb{R}^M$   |  |  |  |  |
| 1: Set $I = (), \mathbf{r} = \mathbf{y}, \mathbf{D}_r = \mathbf{D}(:, I)$                                  |  |  |  |  |
| 2: for target sparsity do  |  |  |  |  |
| 3: $i_{max} = \max_i  \mathbf{D}(:,i)^H \mathbf{r} $   |  |  |  |  |
| 4: $\mathbf{I} = (\mathbf{I}, \mathbf{i}_{max})$   |  |  |  |  |
| 5: $\phi = \text{angle}\{\mathbf{D}(:, i_{max})^H \mathbf{r}\}$  |  |  |  |  |
| 6: $\mathbf{D}_r(:, i_{max}) = \Re\{\mathbf{D}(:, i_{max})e^{-j\phi}\}$                                    |  |  |  |  |
| 7: $\mathbf{x}(I) = \mathbf{D}_r(:, I)^{\dagger} \mathbf{y}$ † denotes pseudo inverse                      |  |  |  |  |
| 8: $\mathbf{r} = \mathbf{y} - \mathbf{D}_r(:, I)\mathbf{x}(I)$   |  |  |  |  |
| 9: end for   |  |  |  |  |
|  |  |  |  |  |

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# 610 Tables

**Table 1:** Ultrasound measurements:  $\Delta t$  is the arrival time difference between the two echoes,  $\Delta f$  is the shift of central frequency,  $\sigma_f$  is related to the frequency bandwidth. The quality factor  $Q_{11}^{-1}$  is calculated from these three quantities and Ct.nBUA is calculated using the ultrasound measurements and Ct.Th measured with Ht-pQCT.

| Subject        | $\Delta t$        | $\Delta f$        | $\sigma_{f}$      | $Q_{11}^{-1}$  | Ct.nBUA                 |
|----------------|-------------------|-------------------|-------------------|----------------|-------------------------|
| No.            | $(\mu s)$         | (MHz)             | (MHz)             | (%)            | $(dB.MHz^{-1}.cm^{-1})$ |
| 1              | $1.67 \pm 0.02$   | $0.21 {\pm} 0.15$ | $0.94{\pm}0.03$   | $5.1 \pm 3.4$  | $3.7{\pm}2.5$           |
| 2              | $1.75 {\pm} 0.04$ | $0.34{\pm}0.13$   | $1.05 {\pm} 0.19$ | $8.4{\pm}2.6$  | $6.5 \pm 2.2$           |
| 3              | $1.70 {\pm} 0.02$ | $0.46 {\pm} 0.07$ | $0.81 {\pm} 0.02$ | $13.5 \pm 3.1$ | $9.5 \pm 2.3$           |
| 4              | $2.14{\pm}0.08$   | $0.51 {\pm} 0.11$ | $0.93 {\pm} 0.06$ | $9.1{\pm}1.8$  | $7.8 {\pm} 1.7$         |
| 5              | $2.32{\pm}0.04$   | $0.37 {\pm} 0.16$ | $0.89 {\pm} 0.06$ | $6.8 \pm 3.6$  | $5.8 \pm 3.1$           |
| mean $\pm$ std | $1.92{\pm}0.30$   | $0.38 {\pm} 0.12$ | $0.92{\pm}0.09$   | $8.6 \pm 3.1$  | $6.7 \pm 2.2$           |

<sup>619</sup> **Table 2:** Cortical thickness (Ct.Th) and volumetric bone mineral density <sup>620</sup> (Ct.vBMD) obtained from HR-pQCT images.

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|                | HR-pQCT           |                       |  |  |  |
|----------------|-------------------|-----------------------|--|--|--|
| Subject No.    | Ct.Th (mm)        | Ct.vBMD $(g.cm^{-3})$ |  |  |  |
| 1              | $3.11 \pm 0.08$   | $1.23 \pm 0.02$       |  |  |  |
| 2              | $3.13 {\pm} 0.02$ | $1.13 \pm 0.02$       |  |  |  |
| 3              | $3.28 {\pm} 0.06$ | $1.06 {\pm} 0.03$     |  |  |  |
| 4              | $3.43 {\pm} 0.02$ | $1.14 {\pm} 0.02$     |  |  |  |
| 5              | $3.79 {\pm} 0.03$ | $1.16 {\pm} 0.03$     |  |  |  |
| mean $\pm$ std | $3.35 \pm 0.28$   | $1.14 \pm 0.06$       |  |  |  |

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|             | Subject No.    | $v_{11} \ (mm.\mu s^{-1})$ |  |  |
|-------------|----------------|----------------------------|--|--|
|             | 1              | $3.72 {\pm} 0.14$          |  |  |
|             | 2              | $3.58 {\pm} 0.10$          |  |  |
| 626         | 3              | $3.86 {\pm} 0.12$          |  |  |
|             | 4              | $3.21 {\pm} 0.14$          |  |  |
|             | 5              | $3.27 {\pm} 0.08$          |  |  |
| 60 <b>7</b> | $mean \pm std$ | $3.53 \pm 0.28$            |  |  |
| 021         |                | ·                          |  |  |

Table 3: Longitudinal bulk wave velocities calculated as  $v_{11} = 2$ Ct.Th/ $\Delta t$ using values given in Tables 1 and 2

Table 4: Normalized broadband ultrasonic attenuation (nBUA) values published in the scientific literature and in this study. Mean values are given, and standard deviation when available.

\* In Talmant et al. (2019), the reported attenuation normal to the direction of osteons is, at 4 MHz, 3.9 dB.cm<sup>-1</sup> per percentage of porosity ; the value given in the table is calculated for a very moderate porosity of 5% characteristic of the bone of a healthy young adult.

| Reference   | Species and<br>skeletal sites                                    | Number of<br>samples | Frequency<br>range or cen-<br>ter frequency<br>(MHz) | $\begin{array}{c} \mathrm{nBUA} & (\mathrm{dB} \\ \mathrm{MHz^{-1}cm^{-1}}) \end{array}$ |
|---|--|----------------------|--|--|
| Lakes et al.<br>(1986)(Lakes et al.,<br>1986)                                 | bovine femur<br>( <i>ex vivo</i> )                               | 1                    | 1-7  | ~3   |
| Lees and Klopholtz<br>(1992)(Lees and<br>Klopholz, 1992)                      | bovine femur<br>( <i>ex vivo</i> )                               | 4                    | 0-30   | ~4   |
| Han et al.<br>(1996)(Han et al.,<br>1996)                                     | bovine femur<br>( <i>ex vivo</i> )                               | 5                    | 0.3-0.7  | 5 - 12   |
| Zheng         et           al.(2007)(Zheng         et           et al., 2007) | bovine femur<br>( <i>ex vivo</i> )                               | 8                    | 2.25   | $4.91 {\pm} 0.65$  |
| Sasso et<br>al.(2008)(Sasso<br>et al., 2008)                                  | bovine femur<br>( <i>ex vivo</i> )                               | 40                   | 3.5-4.5  | 4.2±2.4  |
| Talmant et al. $(2019)$   | $\begin{array}{c} \text{human femur} \\ (ex \ vivo) \end{array}$ | 35                   | 2-8  | 4.9  |
| This paper  | one-third dis-<br>tal radius ( <i>in</i><br><i>vivo</i> )        | 5                    | 3.5  | $6.7 \pm 2.2$  |