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Imaging of thermal effects during high-intensity ultrasound treatment in liver by passive elastography: a preliminary feasibility *in-vitro* study

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Abstract

High-intensity focused ultrasound is a noninvasive modality for thermal ablation of tissues through locally increased temperature. Thermal lesions can be monitored by elastography, following the changes in the elastic properties of the tissue as reflected by the shear-wave velocity. Most studies on ultrasound elastography use shear waves created by acoustic radiation force. However, in the human body, the natural noise due to cardiac activity or arterial pulsatility can be used to characterize elasticity through noise-correlation techniques, as the method known as passive elastography. The objective of this study was to investigate the feasibility of monitoring high-intensity ultrasound treatments of liver tissue using passive elastography. Bovine livers were heated to 80 °C using a high-intensity planar transducer, and imaged with a high-frame-rate ultrasound imaging device. The dynamics of lesion formation are captured through tissue stiffening and lesion expansion.

Keywords: Ultrasound, Elastography, Shear waves, Diffuse wavefield,

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1 Introduction

2 High-intensity focused ultrasound (HIFU) allows noninvasive creation of
3 thermal lesions in deep tissues, and therefore requires techniques to monitor
4 lesion formation.

5 Today, magnetic resonance imaging (MRI) remains the gold standard for
6 monitoring HIFU interventions in the clinic. This provides good anatomical
7 images of tissues and lesions, as well as temperature maps during the inter-
8 ventions (Wu *et al.* , 2001). On the other hand, MRI is not portable, it is
9 expensive, and it has patient and device compatibility issues. Some HIFU
10 devices also integrate ultrasonic imaging. This modality is cheaper, more
11 easily available, and more portable than MRI imaging (Ebbini & Ter Haar,
12 2015). This method allows acquisition with high spatial and temporal reso-
13 lution that provides B-mode images as well as thermal mapping, along with
14 the use of contrast agents to monitor the exposure after treatment. Tech-
15 niques directly based on ultrasound measurements can be based on changes
16 in the characteristics of the compression waves (Anand & Kaczkowski, 2004).
17 Ultrasound thermometry has also been investigated using various ultrasound
18 characteristics, such as the speed of sound (Bayat *et al.* , 2015), the nonlin-
19 earity coefficient B/A (Choi *et al.* , 2011), and the backscattered coefficient
20 (Ghoshal *et al.* , 2016). However, to date, techniques based on changes
21 in the speed of sound have been limited to temperatures below 55°C. The
22 coefficient B/A appears to increase linearly as a function of temperature *in*
23 *vitro*, although as it requires a transmission measurement device, it cannot
24 be measured *in vivo* (Choi *et al.* , 2011). Ultrasound monitoring techniques
25 based on backscattered signals have also been studied, such as backscattered

energy techniques, which have already been implemented for commercial devices (Sanghvi *et al.* , 2017; Zhou, 2017). However, so far, this technique allows for efficient monitoring, while it cannot be used for thermal measurements.

Alternatively, thermal lesions induce changes to the elasticity of a medium, thus allowing elastography to be used to monitor HIFU treatment. This method consists of measuring the shear-wave velocity, which is directly linked to the tissue elasticity. In this domain, the same difficulties as described above are found between magnetic resonance elastography and elastography using ultrasound imaging. Different techniques to observe and create shear waves have been described in the literature (Parker *et al.* , 2011; Tanter & Fink, 2014; Giammarinaro *et al.* , 2018). The most commonly used technique consists of using the acoustic radiation force to create a shear-wave source in the medium. Shear waves are then imaged using a high-frame-rate ultrasound scanner (Bercoff *et al.* , 2004). This technique has already been applied to muscle and liver, in 2010 by Sapin-de Brosses *et al.* (2010). Arnal *et al.* (2011) presented a method for shear-wave thermometry in different tissue samples, although this method was only accurate at temperatures below 55 °C.

Methods based on acoustic radiation force are limited when creating the required shear waves in deep tissues. However, the development of passive methods might solve this issue. The ability to perform elastography would mainly rely on the imaging technique for the shear-wave monitoring. Passive elastography was developed recently, and it is based on noise-correlation techniques. Noise-correlation techniques were first used in seismology to

51 retrieve impulse responses (Aki & Richards, 2002), and therefore the Green's
52 function, in a medium (Sanchez-Sesma, 2006). These techniques have also
53 been studied from a time-reversal point of view, in cavities and in open media
54 (Derode *et al.* , 2002).

55 This method was applied to characterize muscle by Sabra *et al.* (2007),
56 and it was modified for two-dimensional imaging by Gallot *et al.* (2011).
57 Catheline *et al.* (2013) reported on a new algorithm to estimate the shear
58 elasticity using high-frame-rate imaging (Sandrin *et al.* , 1999) and classical
59 low-frame-rate imaging. This latter has also been used for the brain with
60 MRI (Zorgani *et al.* , 2015), for the cornea with optical tomography (Nguyen
61 *et al.* , 2016), and for cells (Grasland-Mongrain *et al.* , 2018). As passive
62 elastography has only been developed recently, its feasibility for HIFU mon-
63 itoring has not been investigated, to the best of our knowledge. In the
64 literature, different organs have been studied for HIFU therapy, as reviewed
65 by (Maloney & Hwang, 2015). The liver is an interesting organ to use for
66 this feasibility study, because it is already a well-studied organ. It has been
67 characterized in terms of elasticity through axial-shear-strain elastography
68 (Thittai *et al.* , 2010), shear-wave elastography (Sapin-de Brosses *et al.* ,
69 2010; Arnal *et al.* , 2011), and MRI (Righetti *et al.* , 1999). However, the
70 most important point is that the *in-vivo* feasibility for passive elastography
71 imaging of the liver has already been demonstrated by (Gallot *et al.* , 2011).
72 This thus defined the objective of the present study, which was to evaluate
73 the feasibility of monitoring thermal lesion formation in liver tissue from 37
74 °C to 80 °C by passive elastography. In this regard, this preliminary experi-
75 mental study was performed with bovine liver, and with a planar transducer

76 as the treatment device. This study is thus devoted to evaluation of the
77 feasibility of monitoring changes during high-intensity ultrasound treatment
78 by imaging elasticity.

79 **Material and methods**

80 *Experimental configuration.* The set-up is illustrated in Figure 1, and it was
81 built to perform high-intensity ultrasound treatments *in vitro*, with a planar
82 transducer placed above the sample holder. An unfocused transducer was
83 chosen to generate wide exposure, which is considered to be homogeneous at
84 the imaged depth, and is slow enough to perform several imaging acquisitions
85 during the treatment. The increased temperatures can be considered to
86 be more homogeneous using this set-up. A linear transducer array that is
87 connected to a high-frame-rate ultrasound scanner is positioned on the side
88 of the sample holder, to image the tissue samples. The temperatures were
89 monitored using a needle thermocouple (29/5; Physitemp Instruments LLC,
90 Clifton, NJ, USA) positioned just above the center of the imaging plane. The
91 experiments were performed in a water-filled tank. The water was degassed,
92 and homogeneously heated to 37 °C using a thermostat (Polystat 36; Fisher
93 Scientific, Hampton, NH, USA), to mimic the physiological conditions of the
94 human body. The thermostat was turned off during interventions to avoid
95 the creation of global motion of the sample through water waves. An external
96 shaker (Model K2004E01; The Modal Shop Inc., Cincinnati, OH, USA) was
97 used to simulate a diffuse wavefield in the tissues samples. Each aspect of
98 the experimental procedures is described further in the following sections.

99 *Tissue preparation.* Bovine livers were collected from a local slaughter house.
100 They were sliced into rectangular prisms of 10 cm x 3 cm x 6 cm with a
101 scalpel, and then stored in a freezer. The pieces of liver tissue were defrosted
102 in a fridge 1 day before each experiment. For each intervention, each tis-
103 sue sample was placed in degassed water with 4 mg/L oxygen, and degassed
104 in a vacuum chamber for 45 min. The aim was to avoid the formation of
105 hyperechogenic microbubbles within the tissue (Bamber & Hill, 1979). A
106 tissue sample was then placed in a custom-made holder, with measurements
107 taken with a multi-element ultrasound imaging probe (L7-4; Philips, Ams-
108 terdam, The Netherlands) coupled to the ultrasound system (Vantage 256;
109 Verasonics, Kirkland, WA, USA).

110 *Lesion formation.* The temperature increases were generated by a 3-MHz
111 home-made piezo-composite plane transducer with a circular effective surface
112 of 126 mm². The probe was powered by a signal generator (programmable 15-
113 MHz function generator HM8131-2; Hameg Instruments, Mainhausen, Ger-
114 many) which was amplified by a 55-dB power amplifier (41501; ADECE,
115 Artannes, France). An acoustic power of 2.4 W was emitted by the therapy
116 probe. The energy of the amplified signal supplied to the probe was moni-
117 tored with a wattmeter (power reflection meter NAP; Rohde & Schwartz, Mu-
118 nich, Germany). The temperature of the transducer was controlled by a cool-
119 ing system (Ablapack & Ablasonic, Edap TMS, Vaulx-en-Velin, France) that
120 included a peristaltic pump (model 7518-60; Masterflex, Bèlignieux, France)
121 and a minichiller (RC6; LAUDA-Brinkmann, LP., Delrann NJ, USA). The
122 temperature in the tissue sample increased from 37 °C up to 80 °C. The av-
123 erage increase in temperature was 3 °C/min. The tissue was then allowed

124 to cool down naturally to 40 °C. The heating was interrupted for 7 s every
125 minute to perform the ultrasonic acquisitions (see Figure 2).

126 *Passive elastography and imaging.* Shear-wave velocity measurements were
127 performed using a method developed by Catheline *et al.* (2013), as modified
128 for the present study (see Appendix). This was based on a time-reversal tech-
129 nique that is also known as 'noise correlation', which allows for the retrieval
130 of the Green's function from a diffuse wavefield (Sanchez-Sesma, 2006).

131 This technique requires the image acquisition to be at a high enough
132 frame rate to meet Shannon's criterion. An ultrasound scanner (Vantage
133 256; Verasonics, Kirkland, OH, USA) was used, which was coupled to a
134 linear transducer array (L7-4; Philips, Amsterdam, The Netherlands). The
135 ultrasound scanner was fully controlled using Matlab 2013a (Mathworks,
136 Natick, MA, USA). An empirical numerical apodisation A was applied to
137 the 128 elements using the Matlab function *tukeywin*, such that:

$$A = 0.5 * \text{tukeywin}(128, 0.2) + 0.5.$$

138 Each imaging sequence was composed of 300 images. These were acquired at
139 600 frames/s from plane waves (Sandrin *et al.* , 1999) emitted at five different
140 angles between $\pm 10^\circ$, to perform the compounding method (Montaldo *et al.*
141 , 2009). At the beginning of each sequence, the external shaker received a
142 synchronizing trigger signal from the ultrasound scanner. This emitted a
143 sinusoidal signal that lasted 1 s, at a frequency of 60 Hz for a voltage of 1 V
144 peak to peak. This frequency was chosen to be in the frequency bandwidth
145 measured in previous liver experiments (Gallot *et al.* , 2011). The ultrasound
146 images were then stored as in-phase and quadrature (IQ) data and the Loupas

147 phase-based motion estimator (Pinton *et al.* , 2005; Lindop *et al.* , 2008; Deng
148 *et al.* , 2017) was used to estimate the particle velocity of the tissue between
149 each ultrasound image. The displacement calculations were performed over
150 windows of two ultrasonic wavelengths. Therefore, for each elasticity map
151 calculated, 300 ultrasound images were used to obtain 299 particular velocity
152 maps. This method allowed the shear-wave velocity map to be obtained over
153 approximately 30 s, and therefore to observe the elasticity changes during
154 the treatment. The choice of 1 min between acquisitions was made based on
155 the calculation times.

156 **Results and Discussions**

157 *High-intensity treatments*

158 The experiments were performed on eight bovine liver tissue samples.
159 Each treatment resulted in the formation of a lesion that was macroscopi-
160 cally visible as a local color change of the tissue. The lesions created in the
161 tissue samples were sliced along the imaging plane. Corresponding images
162 are presented in the third column of Figures 3 and 4. The treated zones
163 were harder to the touch, by palpation, than the untreated liver tissue. The
164 images in Figures 3 and 4 also show that wide lesions (approximately 35 mm
165 x 45 mm) were created using the unfocused plane transducer, as expected.
166 Furthermore, the heat deposit appeared to be relatively homogeneous during
167 the experiments, as the lesions were wide and relatively uniform. In several of
168 the images taken immediately after the treatments, the exposure appeared
169 lighter than the untreated area. A pink border was sometimes observed
170 around the treated area just after the treatment, although this disappeared

171 after a couple of minutes. Chu & Dupuy (2014) explained that lesions *in vivo*
172 are composed of a central zone, which corresponds to irreversible coagulative
173 necrosis, and a peripheral zone that is subjected to sublethal damage, and
174 which contains a large quantity of blood. The *in-vitro* phenomenon might
175 be the result of damage before coagulation around the coagulated area, com-
176 bined with blood expulsion from the exposed area. Moreover, this peripheral
177 zone was also observed in the shear-wave velocity maps that are described in
178 more detail in the following section.

179 *Imaging method for the shear-wave field and time reversal*

180 During the experiments, shear waves were created with an external vi-
181 brator that hit the sample holder. The vibration transmitted through the
182 plastic structure perfectly propagated through the liver tissue as shear waves.
183 The particle velocities due to these shear waves were then estimated using
184 an ultrafast ultrasound scanner. A typical example of a shear-wave field is
185 shown in Figure 5, where four time points are shown for a shear-wave front
186 over 5 ms in sample 1. The shear-wave propagation through the sample can
187 be seen over 500 ms with a frame rate of 600 Hz. Thus, using correlation,
188 a coherence function (or time-reversed focal spot) was computed. The pas-
189 sive elastography algorithm consisted of studying the properties of this focal
190 spot. Its size, or radius of curvature, is directly linked to the shear-wave
191 wavelength (Brum *et al.* , 2008; Gallot *et al.* , 2011; Benech *et al.* , 2013).
192 Figure 6 shows typical focal spots, where the location is estimated by the
193 white cross for sample 3 before and after treatment. We can see that the fo-
194 cal spot becomes much larger, which indicates an increase in the shear-wave
195 velocity in the treated tissue. The shapes of the focal spots greatly depend

196 on the elastic heterogeneities of the samples. The global expansion seen is in
197 agreement with a global increase in elasticity.

198 The possibility of locally estimating the Green’s function shape confirms
199 this use of the passive elastography algorithm (summarized in Appendix). As
200 a result, the shear-wave speed can be estimated for every point by moving
201 the position (marked by a white cross) where the focal spot properties are
202 calculated. This position corresponds to the pseudo-source \vec{r}_0 , as defined in
203 the Appendix in Equation 1. It should also be kept in mind that the wave-
204 speed measurements are conducted in the vicinity of the focal spot maximum,
205 where the signal-to-noise ratio is largest.

206 In this study, it is acknowledged that there is no natural noise, and thus
207 the waves were created using an external shaker. During *in-vivo* experiments,
208 natural noise arises due to cardiac activity and arterial pulsatility. This latter
209 has already been used for the brain (Zorgani *et al.* , 2015). The shear waves
210 presented here were created with a central frequency of around 60 Hz. In
211 the literature, measurements have already been performed *in vivo* by (Gallot
212 *et al.* , 2011). Moreover, during actual *in-vivo* experiments, respiratory mo-
213 tion needs to be taken into account, because this motion can lead to errors
214 in the shear-wave speed estimation and map reconstruction.

215 *Imaging by passive elastography during high-intensity treatments*

216 Each experiment lasted approximately 1 h. Every minute during the
217 heating and cooling periods, for a break of 7 s, the shear-wave velocity maps
218 were computed using the passive elastography algorithm. These results are
219 presented as Videos 1-8, which correspond to samples 1 to 8, respectively.
220 Each movie is thus composed of all of the shear-wave velocity maps obtained

every minute over 45 min, and the temperature at the center of the image is indicated in the title of each frame. On top of this, the black line represents the whole region where the elasticity changes are visible.

In each movie, the tissue within the region of interest (ROI) appears to become stiffer during the heating phase, and more stable during the cooling phase. However, the thermal lesion formation is not always the same. Some movies show spatially uniform increases in the shear-wave velocity during the heating, which suggests that the heating was homogeneous. Other movies show tissue stiffness spreading over time from a point source. Throughout this spreading of the stiff region, a softer border can be seen. This phenomenon is shown in Figure 7, which shows three shear-wave velocity maps that were calculated every minute. It appears that on the first map, two stiffer parts were surrounded by softer borders, which eventually merged during the lesion formation. This phenomenon might have the same explanation as the pink border seen in the photographs presented in Figures 3 and 4. This border would indicate a softer part of the tissue during the experiment, and would still be observable immediately after the treatment.

Lesions detected by passive elastography

In the previous section, we showed the shear-wave velocity maps that were calculated during the treatments, where increases in velocity were seen. These shear-wave velocity maps before and after the treatments are shown in the first and second columns, respectively, of Figures 3 and 4.

For every sample, an increase in shear-wave velocity was seen, which is in agreement with Videos 1-8. With the exceptions of samples 5 and 6, the wide stiff regions appear to correspond to the lesions observed in the third

column of Figures 3 and 4. However, it is important to consider that the experimental ultrasound imaging planes might have been slightly different from the photographs presented in the previous sections. Despite our efforts, cutting through the samples to reveal a surface that perfectly coincided with the imaging plane was challenging. Contrary to other samples, samples 5 and 6 have no clear lesion in the photographs. However, the stiffness appears to be higher post-treatment than pre-treatment in these samples. This is an encouraging result for the feasibility of monitoring lesion formation. For every sample, an irreversible change was detected.

Average shear-wave velocity in the lesions

For all of the experiments, the ROIs displayed in Figures 3 and 4 were used to calculate the average shear-wave velocities on a minute-by-minute basis. These are displayed on the third column of Figures 3 and 4. With the ROIs selected afterwards, dynamic effects on the shapes of exposures were also involved in the average velocity change. The shapes and sizes of the ROIs changed as they were adapted to each observable lesion.

Similar tendencies can be observed for each sample. During the heating period, the shear-wave velocity was relatively stable, sometimes showing a small increase or decrease. From around 45°C, the shear-wave velocity was strongly modified, until the maximum temperature was reached for each experiment. During the subsequent cooling phase, a plateau was observed that corresponds to the final maps shown in the corresponding Figure. The stability of the velocities before reaching 45°C and the plateau after heating appear to show that the effects of the ultrasound are mainly irreversible effects that change the elasticity and nature of the soft tissues. These results

271 are consistent with experiments from Sapin-de Broses *et al.* (2011) that
272 showed similar tendencies for the evolution of the shear modulus as a function
273 of the temperature.

274 However, some differences can be highlighted between the experiments.
275 The first concerns the maximum temperature, which can be caused by differ-
276 ent effects. First, although the ultrasound intensity was set to be constant,
277 the shape of the samples varied. Thinner samples enhanced the heat ex-
278 change with the thermal bath, and were thus prevented from reaching higher
279 temperatures in the tissue. Moreover, the blood vessels in the samples can
280 prevent high temperature increases (see Figures 3 & 4). Indeed, the tempera-
281 ture increases are caused by tissue absorption. However, in the tissue, there
282 are still some blood vessels and bile ducts, which are full of water here. If
283 these are in the high-intensity ultrasound beam, less heat is generated by the
284 ultrasound due to the weak absorption of this water. Moreover, this implies
285 that the tissue is highly heterogeneous, with large impedance differences that
286 can induce some large scattering effects, and thus beam deformations.

287 Another visible difference concerns the behavior observed for each curve.
288 The general tendency previously described is well followed by samples 3,
289 4, 7, and 8. However, even though samples 1, 2, 5, and 6 followed the
290 tendencies already reported in the literature, they present some variations in
291 their behaviors. During the heating phase, the behavior was less monotonous,
292 and it even corresponded to a decrease in the shear-wave velocity for samples
293 1 and 6.

294 These might be explained by tissue motion. During the temperature
295 changes, the tissues suffer from mechanical deformation, such as dilatation

296 or contraction. Therefore, the measurements might have been performed un-
297 der pre-stressed conditions (*i.e.*, stress created by the sample holder), which
298 would modify the shear-wave velocity measured (Gennisson *et al.* , 2007)
299 through acoustoelastic effects. Moreover, tissue deformation can induce mo-
300 tion of the sample, and therefore of the imaging plane. This might explain
301 some of the movements observed in the movies and the discontinuity in sam-
302 ple 5. Another possibility to explain the differences between the experiments
303 would be the dynamic effects: several lesions were created at the same time
304 for sample 7, and they merged to form a single wider lesion. This highlights
305 one of the advantages of the present technique, as it corresponds to imag-
306 ing of the formation of the lesion, thus characterizing its spatio-temporal
307 dynamics.

308 Furthermore, some differences can be observed between samples 4 and 8.
309 The maximum measured temperatures were in both cases around 70°C, but
310 the estimated shear-wave velocities were different. This might be explained
311 by the position of the thermocouple, which might have induced some errors
312 for the temperature estimation. This might also come from differences in the
313 sample shapes, as previously indicated. Indeed, the maximum temperature
314 might have been the same, but might not have been reached over the same
315 duration of time.

316 Conclusions

317 In the present study, the aim was to investigate the feasibility of HIFU
318 monitoring by passive elastography. As such, eight bovine liver tissue sam-
319 ples were treated *in vitro* by ultrasound. In each case, the experiments were

320 successfully imaged by passive elastography during the heating and cooling.
 321 Shear-wave velocity changes were observed during the lesion formation for a
 322 $4 \times 4 \text{ cm}^2$ area. The imaging experiments allowed for observation of the phys-
 323 ical changes during these treatments. The dynamics of the lesion formation
 324 were characterized: the creation of small lesions at different positions, which
 325 then spread in size over time until they fused into wider lesions. Other lesions
 326 showed individual expansion over time. Moreover, the imaged dynamics are
 327 similar to those described in the literature, as shown by the estimations of
 328 the average shear-wave velocities. These first results are encouraging for such
 329 imaging and characterization of the exposure generated by ultrasound in soft
 330 tissues. However, present experiments being *in vitro*, the *in-vivo* feasibility
 331 should be investigated further to allow for using natural vibrations , as well
 332 as the role of perfusion.

333 **Appendix: The passive elastography algorithm**

334 The method described here is based on the paper from Catheline *et al.*
 335 (2013) and uses a time-reversal method to estimate the shear-wave velocity
 336 in the medium. This algorithm is based on the possibility to retrieve the
 337 Green's function through noise correlation from a diffuse wavefield (Sanchez-
 338 Sesma, 2006).

339 Given a diffuse wavefield in an isotropic homogeneous solid measured
 340 along the z-axis, the respective displacement is $u_3(\vec{r}, t) = \phi(\vec{r}, t)$, where \vec{r} is
 341 the position and t is the time. The corresponding time-reversed function is
 342 defined as the convolution over time by:

$$\Phi^{TR}(\vec{r}_0, \vec{r}, \tau) = \phi(\vec{r}_0, -t) \otimes \phi(\vec{r}, t). \quad (1)$$

343 With differentiation over the source point locations \vec{r}_0 and \vec{r} , the time-
 344 reversed field leads to:

$$\frac{\partial^2 \Phi^{TR}}{\partial \vec{r}_0 \partial \vec{r}} = \frac{\partial \phi}{\partial \vec{r}_0}(\vec{r}_0, -t) \otimes \frac{\partial \phi}{\partial \vec{r}}(\vec{r}, t) \quad (2)$$

345 Moreover, the time-reversed function $\Phi^{TR}(\vec{r}_0, \vec{r}, \tau)$ is linked to the Green's
 346 function, which only depends on $\vec{R} = \vec{r} - \vec{r}_0$ in a homogeneous and isotropic
 347 medium. This can be defined by $\Phi^{TR}(\vec{r}_0, \vec{r}, \tau) = \Phi^{RT}(\vec{R} = \vec{r}_0 - \vec{r}, \tau)$. This
 348 new definition implies that:

$$\frac{\partial^2 \Phi^{TR}}{\partial \vec{r}_0 \partial \vec{r}} = -\frac{\partial^2 \Phi^{TR}}{\partial \vec{R}^2}, \quad (3)$$

349 and therefore,

$$\frac{\partial^2 \Phi^{TR}}{\partial \vec{R}^2} = -\frac{\partial \phi}{\partial \vec{r}_0}(\vec{r}_0, -t) \otimes \frac{\partial \phi}{\partial \vec{r}}(\vec{r}, t). \quad (4)$$

Assuming a monochromatic wavefield, the time-reversal field is related to the
 Green's function in the Fourier domain by:

$$\begin{aligned} \tilde{\Phi}^{TR}(\vec{r}_0, \vec{r}, \omega) &= \tilde{\phi}^*(\vec{r}_0, \omega) \tilde{\phi}(\vec{r}, \omega) \\ &\propto \text{Im} \left[G_{33}(\vec{R} = \vec{r}_0 - \vec{r}, \omega) \right] \end{aligned} \quad (5)$$

The described method is based on the near field of the Green's function,
 which can be approximated by Benech *et al.* (2013):

$$\begin{aligned} \tilde{\Phi}^{TR}(0, \vec{r}, \omega) &\propto \frac{k}{12\pi\mu} \\ &\left\{ \left(\frac{\beta}{\alpha} \right)^3 \left(1 - \frac{(qr)^2}{10} \right) + 2 \left(1 - \frac{(kr)^2}{5} \right) \right. \\ &\quad \left. + \frac{1}{5} \left[(kr)^2 - \left(\frac{\beta}{\alpha} \right)^3 \right] \cos^2(\theta) \right\} \end{aligned} \quad (6)$$

where μ is the shear modulus, α and β are the compression and shear-wave velocities, respectively, q and k are their respective wave numbers, and θ is the angle between the z-axis and \vec{r} .

Equation 6 shows that the amplitude of the time-reversed field is related to:

$$\tilde{\Phi}^{TR}(0, 0, \omega) \propto \frac{k}{6\pi\mu} \quad (7)$$

and for the case of the strain along a line:

$$-\frac{\partial^2 \tilde{\Phi}^{TR}}{\partial R^2}(0, 0, \omega) \propto (2 - \cos^2 \theta) \frac{k^3}{30\pi\mu} \quad (8)$$

Considering the time-reversed strain function ζ_z^{RT} and ζ_x^{RT} defined in Catheline *et al.* (2013), respectively, along the z and x axes:

$$\tilde{\zeta}_z^{TR}(\vec{R} = 0, \omega) \propto \frac{k^3}{30\pi\mu} \quad (9)$$

$$\tilde{\zeta}_x^{TR}(\vec{R} = 0, \omega) \propto 2 \frac{k^3}{30\pi\mu} \quad (10)$$

$$\begin{aligned} & \tilde{\zeta}_z^{TR}(\vec{R} = 0, \omega) + 2\tilde{\zeta}_x^{TR}(\vec{R} = 0, \omega) \\ & \propto \frac{k^3}{6\pi\mu} \end{aligned} \quad (11)$$

The time-reversed particle velocity is given by:

$$V^{TR}(\vec{r}_0, \vec{r}, \tau) = \frac{\partial \phi}{\partial t}(\vec{r}_0, -t) \otimes \frac{\partial \phi}{\partial t}(\vec{r}, t). \quad (12)$$

In using the derivative properties of the convolution, the previous equation results in the time-reversed particle velocity at position \vec{r}_0 being defined as:

$$V^{TR}(\vec{R} = 0, \tau) = -\frac{\partial^2 \Phi^{TR}}{\partial \tau^2}(\vec{R} = 0, \tau) \quad (13)$$

361 and in the Fourier domain, it can be approximated by:

$$\tilde{V}^{TR}(\vec{R} = 0, \omega) \propto \frac{\omega^2 k}{6\pi\mu} \quad (14)$$

362 Previous calculations were performed in the Fourier domain. However,
363 under the assumption of a monofrequency signal, they are still accurate in
364 the time domain. This leads to the possibility to estimate the shear-wave
365 velocity as:

$$c = \frac{\omega}{k} = \sqrt{\frac{V_0^{TR}}{\zeta_z^{TR} + 2\zeta_x^{TR}}} \quad (15)$$

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482 **Figure Captions**

483 **Figure 1:** Schematic display of the experimental set-up. A bovine liver
484 sample is positioned in a sample holder in a water tank. The liver tissue
485 is treated from above by a high-intensity ultrasound plane transducer,
486 and imaged from the side using a high-frame-rate ultrasound scanner
487 coupled to a linear transducer array.

488 **Figure 2:** Time-line diagram of a monitored experiment. The high-intensity
489 ultrasound treatment and imaging are coupled so that the treatment
490 continued for 1 min and was then paused for 7 s, to allow the imaging.
491 This procedure was repeated every 1 min during the heating, and the
492 imaging continued during the cooling.

493 **Figure 3:** Experimental results for samples 1 to 4. Shear-wave velocity
494 maps before (left) and after (center left) the treatments. Center right:
495 the average shear-wave velocities estimated during the treatments of the
496 region of interest delimited by the white borders. Right: photographs
497 of the treated samples.

498 **Figure 4:** Experimental results for samples 5 to 8. Shear-wave velocity
499 maps before (left) and after (center left) the treatments. Center right:
500 the average shear-wave velocities estimated during the treatments of the
501 region of interest delimited by the white borders. Right: photographs
502 of the treated samples.

503 **Figure 5:** Shear-wave particle velocity maps that were estimated succes-
504 sively for sample 1 at different times, for a frame rate of 600 Hz. Ex-

505 amplitudes of waves are seen to pass from one side to the other of the
506 tissue sample. The wave fronts are shown by the lines crossed by white
507 arrows, which indicate the direction of their propagation.

508 **Figure 6:** Focal spot of the time-reversed signal calculated for a pseudo-
509 source displayed as a white cross for sample 8 before (left) and after
510 (right) the treatments. The size of the focal spot was increased by the
511 high-intensity treatment.

512 **Figure 7:** Snapshot of the shear-wave velocity maps at different tempera-
513 tures for sample 7. Softer borders can be seen, and are indicated by
514 the dotted line.

515 **Video Captions**

516 **Video 1:** Shear-wave velocity maps for every temperature (given as the front
517 title) for sample n°1.

518 **Video 2:** Shear-wave velocity maps for every temperature (given as the front
519 title) for sample n°2.

520 **Video 3:** Shear-wave velocity maps for every temperature (given as the front
521 title) for sample n°3.

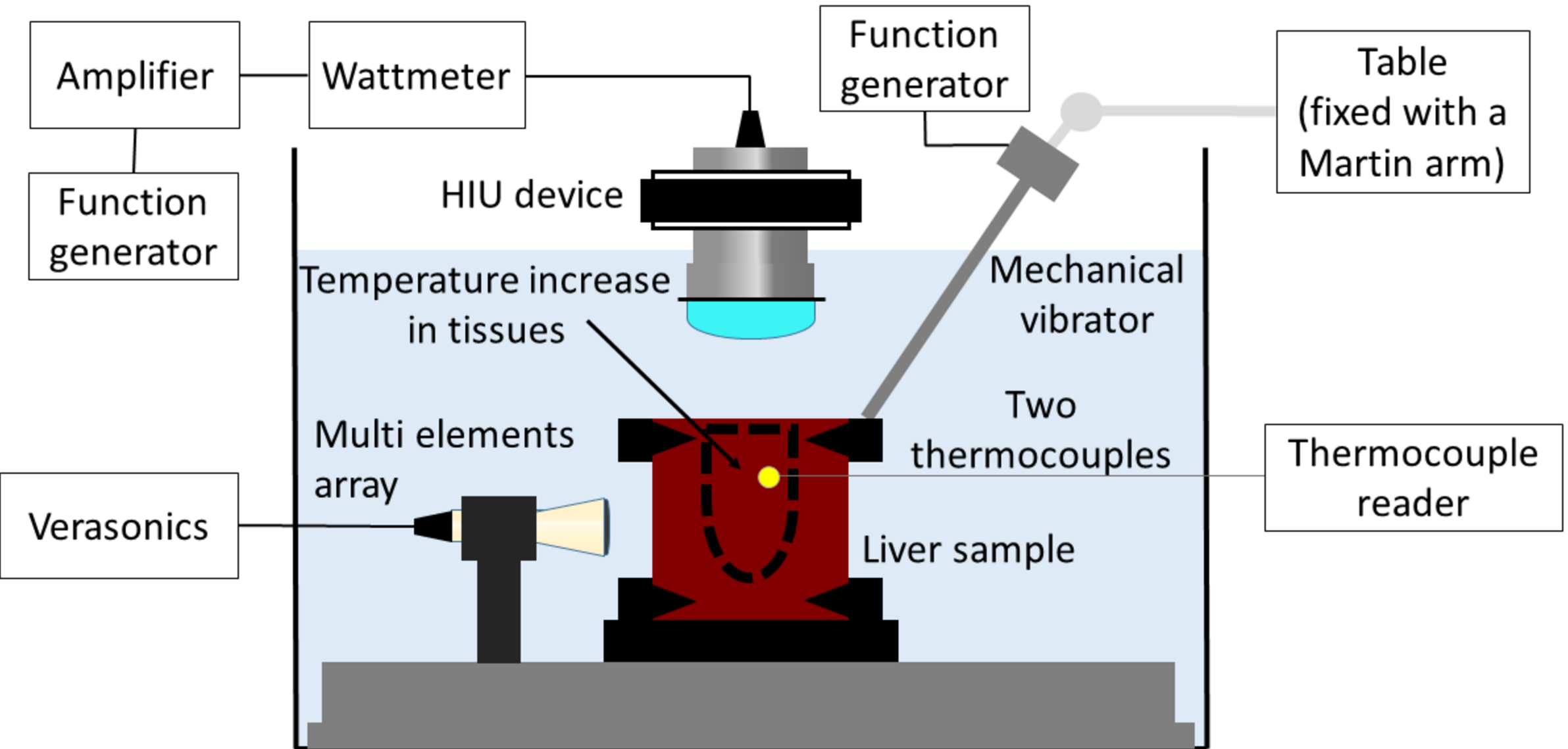
522 **Video 4:** Shear-wave velocity maps for every temperature (given as the front
523 title) for sample n°4.

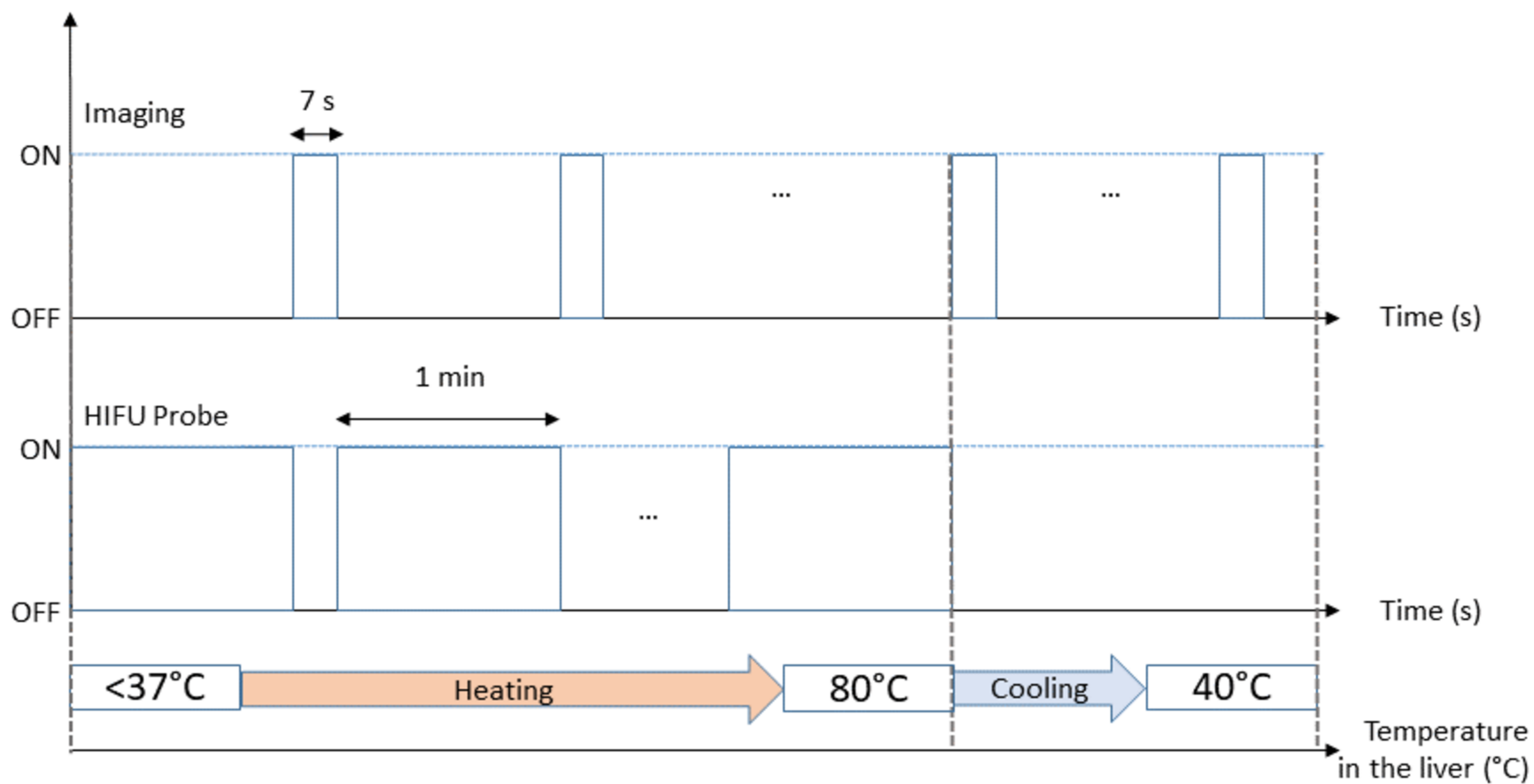
524 **Video 5:** Shear-wave velocity maps for every temperature (given as the front
525 title) for sample n°5.

526 **Video 6:** Shear-wave velocity maps for every temperature (given as the front
527 title) for sample n°6.

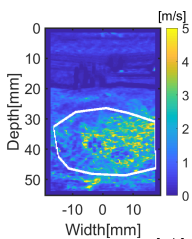
528 **Video 7:** Shear-wave velocity maps for every temperature (given as the front
529 title) for sample n°7.

530 **Video 8:** Shear-wave velocity maps for every temperature (given as the front
531 title) for sample n°8.

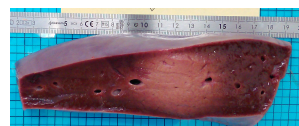
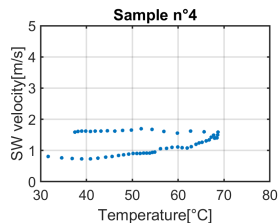
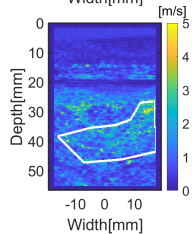
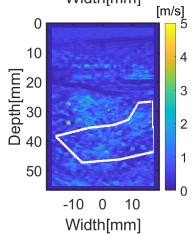
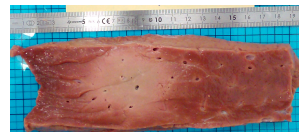
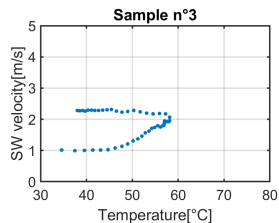
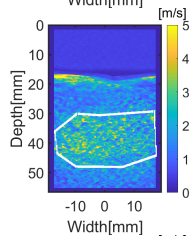
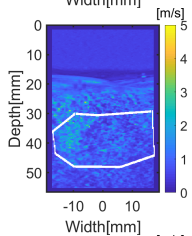
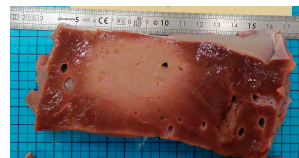
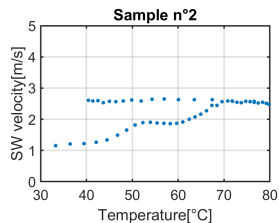
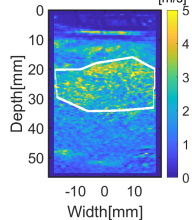
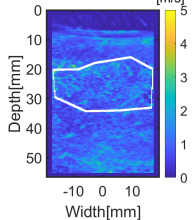
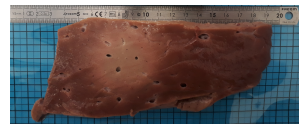
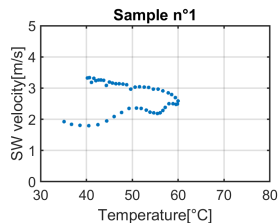
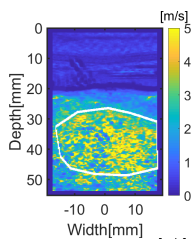




Before



After



Before

After

