

1 **TITLE PAGE**

2 **Title**

3 CLINICAL FEASIBILITY OF QUANTITATIVE ULTRASOUND TEXTURE ANALYSIS: A ROBUSTNESS
4 STUDY USING FETAL LUNG ULTRASOUND IMAGES

5

6 **Manuscript category**

7 Original research

8

9 **Author names and affiliation**

10 *Alvaro Perez-Moreno^{1,2}, MS, Mara Dominguez¹, MS, Federico Migliorelli^{2,3}, MD, Eduard*
11 *Gratacos^{2,3,4}, MD, PhD, Montse Palacio^{2,3,4}, MD, PhD, Elisenda Bonet-Carne^{1,5}, PhD*

12 ¹ Transmural Biotech S.L. Barcelona, Spain.

13 ² Fetal i+D Fetal Medicine Research Center, IDIBAPS, University of Barcelona, Spain.

14 ³ BCNatal – Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital Clínic and
15 Hospital Sant Joan de Deu), Barcelona, Spain

16 ⁴ Center for Biomedical Research on Rare Diseases (CIBER-ER), Barcelona, Spain

17 ⁵ UCL - Microstructure Imaging Group, Centre for Medical Image Computing (CMIC), London,
18 United Kingdom

19

20 **Short title**

21 Clinical feasibility of ultrasound texture analysis

22

23 **Corresponding author**

24 Alvaro Perez-Moreno

25 alvaro.perez@transmuralbiotech.com

26 Phone +34 931 190 929

27 Sabino Arana, 38 1r 1a – 08028 Barcelona - Spain

28

29

30 **ABSTRACT**

31 **Objectives.** To compare the robustness of several methods based on quantitative ultrasound
32 texture analysis in order to evaluate its feasibility for extracting features from ultrasound images
33 on its use for diagnosis in a clinical tool.

34 **Methods.** We compared, ranked and validated the robustness of five texture-based methods
35 for extracting textural features from ultrasound images acquired under different conditions. For
36 comparison and ranking purposes, we used 13.171 non-ultrasound images from widely known
37 available databases (OUTEX and PHOTEX); specifically acquired under different controlled
38 parameters (illumination, resolution and rotation) from 103 textures. The robustness of those
39 methods with better results using the non-ultrasound images were validated using 666 fetal lung
40 ultrasound images acquired from singleton pregnancies. In this study, two similarity
41 measurements (Correlation and Chebyshev distances) were used to evaluate the repeatability
42 of the features extracted from the same tissue images.

43 **Results.** Three of the five methods presented a favorably robustness performance using the non-
44 ultrasound database. In fact, these methods showed similarity values close to 0 for the
45 acquisition variations and delineations. Results from ultrasound database confirmed robustness
46 for all the evaluated methods when comparing the same texture obtained from different regions
47 of the image (proximal/distal lungs and ultrasound machine brand stratification).

48 **Conclusions.** Our results confirmed that texture analysis can be robust (high similarity for
49 different condition acquisitions) with potential to be included in a clinical tool.

50

51 **Keywords**

52 Quantitative ultrasound, Ultrasonography, Texture analysis, Image processing, Robustness

53

54 **FULL TEXT**

55 **Introduction**

56 Development of non-invasive and reliable methodologies to report pathophysiological
57 process status is still an elusive goal in modern medicine. Texture analysis methods have been
58 extensively investigated on medical images, as they possess a vast amount of texture
59 information relevant to clinical practice.¹ This phenomenon occurs because medical images
60 contain physical properties of tissues; the signal producing the image changes according to
61 modifications of tissue microstructure and composition. Texture analysis methods allow
62 quantification of these subtle changes in the image.¹

63 Over the years, a large number of powerful texture-based methods have been
64 developed thanks to improvements in computation capacity and image resolution.^{2,3,4}
65 Specifically, texture analysis in ultrasound images extracts information related to the speckle
66 characteristics of the ultrasound image. Oosterveld et al.⁵ showed the close relation between
67 speckle and the “density” of the ultrasound scatter within a medium. In that study, Oosterveld
68 et al.⁵ suggested that ultrasound texture analysis could quantify the effective number density of
69 tissues, as well as pathological changes of this parameter. Thus, the principle goal of applying
70 ultrasound texture analysis is to characterize speckle variation between ultrasound images in
71 order to distinguish those tissues altered as a consequence of the pathology.

72 The ability of texture-based methods for extracting relevant texture features from
73 medical ultrasound images and quantifying subtle changes in human tissues, non-visible to the
74 human eye, have been widely demonstrated.^{6,7,8} One of the first studies based on ultrasound
75 texture analysis⁷ presented a perspective on tissue characterization features to extract
76 diagnostic information. Later, Tunis et al.⁸ corroborated that textural information in ultrasound
77 images is related to pathophysiological processes. Thus, the potential clinical application of
78 quantitative ultrasound texture analysis has been investigated in different medical fields.^{9,10,11,12}

79 Sujana et al.¹³ used ultrasound texture analysis and classification methods for characterizing
80 certain liver lesions, Chen et al.¹⁰ for classification of breast tumors and even Vince et al.¹⁴ for
81 characterizing coronary plaques. In the fetal-maternal field, ultrasound texture analysis was
82 introduced to evaluate association of brain textures with neurobehavioral outcome in preterm
83 newborns.¹²

84 Research in other quantitative ultrasound-based techniques reasserts a clinical trend in
85 obtaining information related to tissue microstructure taking advantage of its acoustical
86 properties. These techniques include elastography, flow estimation through Doppler, shear
87 wave imaging, spectral-based parameterization of ultrasound signals and envelope statistics.
88 ^{15,16} Despite some of these techniques have shown promising results for diagnosis purposes,
89 most of them require specific devices and training for its integration into a clinical setting.¹⁶ We
90 introduce quantitative ultrasound texture analysis as a technique that might be easily
91 implemented into clinical practice as it might provide reliable information from standard
92 ultrasound.

93 Up to the present, most of the studies have applied texture-based methods as part of a
94 classification system, where ultrasound texture features fed the classifier, evaluating its
95 performance to predict the clinical outcome.^{17,18} There have been few application-oriented
96 studies aimed to evaluate the relative powers of the texture-extractor methods before any
97 classification or retrieve system. In fact, none of them have considered whether ultrasound
98 texture features are robust enough (i.e. repeatable regardless of different image acquisition
99 parameters, such as illumination or resolution) to be used in a clinical setting. In particular, any
100 have used a huge number of ultrasound images of the same tissue acquired under different
101 conditions. It is worth to consider that speckle characteristics may be affected due to different
102 acquisition conditions including but not restricted to those induced by operators, biological
103 samples or ultrasound system settings. Some quantitative ultrasound-based approaches have
104 attempted to characterize pathological tissues in a robust way^{19,20,21,22} but these require

105 following complicated acquisition protocols to provide repeatable acquisitions conditions in
106 order to replicate the results. Furthermore, there are new texture-based methods that have not
107 been widely applied for characterizing ultrasound texture in the literature^{23,24} even though they
108 might be useful because they compute local textural features related to local information²⁵.
109 Finally, a fundamental step in the use of texture-based methods is the region of interest (ROI),
110 which identifies the region of the image that corresponds to the piece of tissue that will be
111 analyzed. Most studies overlook this step when evaluating texture analysis whereas it is a
112 fundamental step as delineation (selection of the ROI) would be performed by different
113 operators and, therefore, will be different each time. This might also affect the robustness of
114 the specific textural features. For all the above, a robustness assessment to variations in the
115 ultrasound acquisition conditions and delineations of same type of tissue would represent a step
116 forward in the exploration of the use of quantitative ultrasound texture analysis for clinical
117 purposes.

118 We aimed to compare, rank and validate the robustness of several texture-based
119 methods in order to evaluate its feasibility as texture feature extractors in ultrasound images on
120 its use for analysis in a clinical tool. Particularly, we compared methods that compute local
121 information. We included those methods most commonly found in literature for ultrasound
122 texture classification and newer methods as an alternative. To evaluate the methods, we
123 acquired different ultrasound images of the same texture acquired under different conditions.
124 Nevertheless, two main limitations were observed: (1) not all parameters can be modified
125 through the whole range when scanning real textures due to clinical limitations. For instance,
126 different ultrasound wave absorption exists when crossing distinct tissues such as fat or bone
127 causing acoustic shadows; sometimes these artifacts cannot be avoided when the organ of
128 interest is fixed and distant to the transducer (fetal evaluation); and (2) it is not possible to
129 change acquisition parameters in a precise and controlled way especially due to operator
130 variability when positioning the transducer. Thus, we decided to use an approach inspired with

131 the Image Quality Transfer (IQT) one which first selects and configures the methods using images
132 obtained with a different source but that are easier to be acquired in a controlled setting and
133 later the method is refined using real images.²⁶ Concretely, we used two sets of images for this
134 study: (1) a controlled set of images, non-ultrasound available images acquired under controlled
135 acquisition parameters (i.e. illumination, rotation angle) emulating the acquisition conditions of
136 medical ultrasound setting, thus evaluating a huge number of images for each texture, and (2)
137 an ultrasound image set comprising ultrasound images of fetal lungs acquired under similar
138 conditions to those of a clinical setting. Hence, (1) different texture-based methods were
139 compared and ranked using the controlled sample set and (2) the most robust methods were
140 validated using clinically acquired ultrasound images of fetal lungs.

141

142 **Materials and methods**

143 In this section, we briefly describe both (1) image data sets and (2) its characteristics
144 (image acquisition and image labeling) in order to determine which information related to
145 acquisition conditions was evaluated. We also describe (3) the ROIs to evaluate the robustness
146 when different regions of the same tissue are delineated. Then, we introduce (4) the texture-
147 based methods and (5) the metrics used to compare, rank and validate robustness of the
148 methods for acquisitions and delineations. Finally, we describe (6) the experiments' design used
149 in this study.

150 Data Sets

151 *Controlled sample set.* Images with different textures were obtained from widely known
152 available databases that previously have been used for testing classification methods²⁷, OUTEX²⁸
153 and PHOTEX²⁹. These databases provide pictures of the same texture acquired under different
154 conditions varying (1) illumination, (2) spatial resolution and (3) rotation parameters, thus
155 emulating the differences between ultrasound textures when acquired at different conditions
156 in a controlled way. Three parameters whose changes might affect ultrasound speckle patterns
157 and used to be indirectly adjusted by the radiologist when performing ultrasound scanning: (1)
158 illumination, which is related to gain parameter or image contrast and possible attenuation of
159 the acoustic wave that have to cross different tissues till arriving to the desired tissue to be
160 analyzed; we also used illumination for the ultrasound system's colormaps that can be different
161 for different systems since it is inherent to the ultrasound system; (2) spatial resolution that is
162 related to frequency, depth, zoom and the aperture of the transducer and (3) rotation
163 determined by the unpredictable position of the organ and the transducer when performing a
164 scan.

165 *Clinical ultrasound images.* Fetal lung ultrasound images were acquired from singleton
166 pregnancies attending the Maternal-Fetal Medicine Department at Hospital Clinic in Barcelona

167 for routine pregnancy ultrasound scans. Multiple pregnancies and structural/chromosomal
168 anomalies were excluded from the study. Ultrasound images of the same lung tissue acquired
169 at different conditions were not available for all patients since it was not feasible to acquire
170 images with the whole range of acquisition parameters in a precise and controlled way. The
171 study protocol was approved by the local Ethics Committee (ID 3823-2007) and pregnant women
172 provided written informed consent.

173 Image acquisition and labeling

174 Each Data Set was acquired and labeled as follows:

175 *Controlled.* OUTEX and PHOTEX databases were downloaded from the links specified in
176 Hossain et al.²⁷ For the purpose of this study, only those textures that could be similar to the
177 ultrasound patterns (i.e. granulated, dotted, flecked, etc.) were selected by visual inspection. An
178 example of the selected textures is shown in **Figure 1**. Additionally, only those images that
179 presented similar histograms to the ones computed from the real ultrasound textures were
180 selected (see an example in **Figure S.1** in the supplementary material). Analysis of variance
181 (ANOVA) was computed to compare the mean, skewness and kurtosis of the histograms
182 computed from the Controlled and Clinical data sets. All images were digitally stored in Portable
183 Network Graphics (PNG) and Tagged Image File (TIF) formats and converted to gray scale values
184 within a range between 0 and 255 values. Then, texture images were labeled according to
185 controlled acquisition parameters.

186 A total of 69 textures were selected and labeled from OUTEX database obtaining a total
187 of 11178 images. Specifically, OUTEX textures were labeled according to different illuminations
188 (horizon, inca and TL84), that emulate differences in the gain and ultrasound system's colormaps
189 used for ultrasound image representation, the resolution levels (100, 120, 300, 360, 500 and 600
190 dpi) and rotation degrees (0° , 5° , 10° , 15° , 30° , 45° , 60° , 75° and 90°) obtaining 162 images per
191 texture. Changes in resolution and rotation degrees emulate different acquisition conditions
192 that used to be present between ultrasound images due to frequency, depth and/or organ

193 position changes. Regarding the PHOTEX database, a total of 1993 images were labeled from 34
194 tissues selected for the purpose of this study. PHOTEX database images were labeled according
195 to rotation degrees and tilt angles of illumination since they emulate changes in ultrasound
196 textures due to transducer and/or organ position when insonating an organ. The acquisition
197 parameters (rotation and tilt illumination) were controlled but differed for each texture.

198 *Clinical.* Ultrasound images of fetal lungs were acquired in an axial section of the fetal
199 thorax at the level of the cardiac four-chamber view. Acquisition settings as gain, zoom,
200 frequency and time-gain compensation were not fixed and were adjusted according clinical
201 criteria. Depth and the aperture of the transducer were adjusted to magnify the fetal thorax so
202 that the thorax occupied about two thirds of the screen. Aperture might change for each
203 ultrasound system, operator and the unpredictable position of the fetus during acquisition.
204 Changes in aperture and frequency are related to changes in spatial resolution (see its
205 distribution in **Figure S.2** in the supplementary material). Scans were performed by certified
206 radiologists using a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, Pa., USA),
207 Voluson 730 Pro, Voluson 780 Pro (GE Medical Systems, Milwaukee, Wisc., USA), ALOKA
208 Prosound Alpha-7 (Hitachi Aloka Medical, Ltd., Tokyo, Japan) and Toshiba Aplio (Toshiba Medical
209 Systems, Tokyo, Japan) ultrasound system. All machines were equipped with curved linear
210 transducer with a frequency range from 3 to 7.5 MHz. All images were collected digitally in the
211 original Digital Imaging and Communication in Medicine (DICOM) format and then inspected by
212 EB and AP for image quality control. Images were considered non-eligible if fetal thorax occupied
213 less than two thirds of the screen, or if color Doppler, calipers or pointers were used.
214 Furthermore, images were excluded if they presented any of the following characteristics as
215 they can directly alter the values of the ultrasound features: presence of obvious acoustic
216 shadows from the fetal ribs, saturation or any type of post-processing (such as smoothing).
217 Image quality control was done manually assisted by an ad-hoc graphical user interface (GUI)
218 that: (1) computed the proportion of fetal thorax in the image by semi-automatically delineating

219 an ellipse over the thorax, (2) showed images in order to check the use of calipers, color Doppler
220 or any type of post-processing, and (3) plotted acoustic shadows in green and saturated regions
221 in red (pixel values close to 0 and 255, respectively).

222 A total of 713 ultrasound images were acquired from 385 fetuses. 47 images were
223 discarded resulting in 666 useful images from a total of 355 patients after image quality control.
224 Images were labeled according to rotation angle, fetal spine position (left or right) and the
225 proximal lung (the lung close to the transducer) as left or right. The same GUI developed for
226 image quality control was used to label the fetal lungs. By means of the GUI, a clinical expert
227 (FM) semi-automatically calculated rotation angle indicating the orientation of the fetal spine
228 respect to the atrio-ventricular bundle of the heart (see rotation angle distribution in **Figure S.3**
229 in the supplementary material). Additionally, the clinical expert also indicated the fetal spine
230 position and the proximal lung as defined above. The same GUI was used for delineation.

231 Image delineation

232 Once images were labeled, different delineations were performed in each image for
233 each Data Set:

234 *Controlled.* An automatic delineation was performed for each texture image considering
235 (1) 25 non-overlapped and (2) 28 overlapped but with different size ROIs. In this manner,
236 different regions of the same texture were evaluated as it is shown in **Figures 2** and **3**,
237 respectively.

238 *Clinical.* Two operator dependent delineations of both fetal lungs were considered, (1)
239 manually and (2) semi-automatically ROIs, which were performed by a clinical expert (FM)
240 (**Figure 4**). Manual delineations included the largest possible homogenous area of the fetal lung,
241 avoiding the heart, gross vessels and surrounding areas. Semi-automatic delineations were
242 performed indicating a size-fixed squared region, following the same criteria than for manual
243 delineations. After the operator dependent delineations were performed, smaller ROIs were

244 created automatically, eroding repeatedly the manual and semi-automatic delineations (**Figure**
245 **5**) until reaching the limit of 100 pixels for the smallest ROI.

246 Texture-based methods

247 The texture-based methods used for this study are expected to be able to extract gray-
248 scale, multi-resolution and/or rotation invariant local features from ultrasound images, as
249 robustness for these characteristics will be required for their use in a clinical application.
250 Additionally, the number of textural features obtained by each method should not be dependent
251 on the ROI size or location within the same type of tissue. Textural image features were
252 computed by several texture-based methods, widely known for texture classification in the
253 computer vision field.^{2,3,4,23,24} For each texture-based method different sets of textural features
254 were extracted for each ROI and image. The used texture-based methods are detailed below
255 (see a summary of the texture-based methods in **Table S.1** in the supplementary material):

256 *Gray-Level Co-occurrence Matrices (GLCM)*

257 GLCM has been widely used to characterize textures in ultrasound images.^{30,31} This method
258 counts pairs of horizontally adjacent pixels in a grayscale version of the image as defined by
259 Haralick et al.² Characteristics of the features extracted by this method are described in detail
260 elsewhere.² In our experiments, one adjacency direction 0^0 and 8 gray levels when scaling the
261 grayscale values in the image were used to compute GLCM. Thus, there were 64 possible
262 ordered combinations of values for each pair of pixel corresponding to the final 64 textural
263 features.

264 *Local Binary Patterns (LBP)*

265 LBP has been recently applied for texture characterization in ultrasound images.^{32,33} This method
266 computes the distribution of binary patterns in the circular neighborhood of each pixel, which is
267 characterized by a radius R and a number of neighbors P. The principle is to threshold
268 neighboring pixels, compared to the central pixel. Thus, for each pixel a binary pattern is

269 obtained. A LBP code at pixel p is computed by the scalar product between the binary pattern
270 and a vector of powers of two,

$$271 \quad LBP(p) = \sum_{i=0}^{P-1} 2^i \delta(f(q_i) - f(p)) \quad (1)$$

272 Where $f(q_i)$ and $f(p)$ are gray levels of pixels q_i and p , respectively, and δ is the Kronecker
273 function. Then, the histogram of the LBP is used as texture features. The LBP method presents
274 some variants that have been widely used as texture features for medical images.³⁴ In particular,
275 we worked with the multi-resolution gray-scale and rotation invariant approach based on
276 recognizing those binary patterns that occur more often in a texture image than others. These
277 frequent patterns are called uniform patterns and are explained in more detail in Ojala et al.⁴ In
278 our study, uniform patterns were defined with $P = 16$ equally spaced pixels on a circle of radius
279 $R = 1$ resulting in 18 specific texture features.

280 *Histogram of Oriented Gradients (HOG)*

281 HOG might obtain information about the anisotropy of a texture, to determine the predominant
282 directions of a texture.³⁵ Recent studies have applied HOG to characterize textures in ultrasound
283 images.^{36,37} But up to the present the main purpose of applying this method on ultrasound
284 images has been macrostructure detection such as nuchal translucency³⁸ or motion
285 estimation³⁹. We decided to include HOG method in our study since it may provide useful
286 information related to tissue histology. HOG counts frequencies of gradient orientation values
287 in localized portions of an image. The gradient orientation is estimated at every pixel and
288 histogram is computed in order to tell how often the respective gradient direction is present in
289 the image. The specific textural features computed by this method are explained in Junior et al.³
290 For this study, each image to be analyzed (ROI) was divided in 3x3 cells (or portions) of the same
291 size and the number of histogram bins was $N_b = 9$, obtaining 81 textural features.

292 *Local Phase Quantization (LPQ)*

293 LPQ computes quantized phase information of the Discrete Fourier Transform (DFT) but it has
294 not been extensively applied in texture classification for medical images and, even less, for

295 characterizing ultrasound textures. It uses the local phase information extracted by Short Term
296 Fourier Transform (STFT) computed over a rectangular $M \times M$ neighborhood N_p at each pixel
297 position p of the image $f(p)$. The way of obtaining the features is explained in more detail in
298 Ojansivu et al.²³ The same number of specific textural features is always computed, obtaining a
299 total of 256 features for this study.

300 *Rotation invariant LPQ (riLPQ)*

301 The riLPQ acronym corresponds to the rotation invariant approach derived from the LPQ
302 method. riLPQ compensates the rotation of the image that has to be analyzed considering the
303 direction of the characteristics in the examination of the local phase. In this manner, the final
304 textural features extracted should be the same regardless of the image rotation. For more detail,
305 the specific features computed by this method are described in Ojansivu et al.²⁴ A total of 256
306 features are obtained by this method.

307 Similarity measurements / metric distances

308 Robustness was evaluated and validated measuring similarity (or dissimilarity) between
309 two sets of specific textural features, extracted from two images of the same texture acquired
310 at different conditions or acquired under the same conditions (the same image) with different
311 ROI. We used Correlation and Chebyshev distances to compare the texture features because
312 they provide different similarity information that might be useful in order to construct a
313 classification algorithm when developing a clinical application.

314 Correlation distance measures the similarity between the relative shapes of the two
315 features sets. This distance is defined as a measure of statistical dependence between two
316 random sets of features. In our study, the scale of Correlation similarity values was inverted for
317 comparison purposes. Consequently, lower distance indicated more similarity (robustness); if
318 the features were dependent, this measure was 0. Conversely, the features were independent
319 when this measure was 1. The Correlation distance used in this study can be expressed as

320
$$D_{CR}(X, Y) = 1 - \frac{\sum_{i=1}^n (X_i - \hat{X})(Y_i - \hat{Y})}{\sqrt{\sum_{i=1}^n (X_i - \hat{X})^2 \sum_{i=1}^n (Y_i - \hat{Y})^2}}, \quad (2)$$

321 where $X = \{X_0, X_1, \dots, X_{n-1}\}$ and $Y = \{Y_0, Y_1, \dots, Y_{n-1}\}$ are the features vectors extracted from images
 322 acquired under different conditions or different delineations considered statistically
 323 independent.

324 Chebyshev distance measures similarity between absolute values. In this study, we
 325 normalized distance between 0 and 1 for comparison purposes, in this manner two sets of
 326 features were similar (robust) if the distance was close to 0 or not (distance close to 1). This
 327 similarity measurement can be expressed as

328
$$D_{CH}(X, Y) = \frac{\max_{0 \leq i \leq N} \{|X_i - Y_i|\}}{\max\{D_{CH}(X, Y)\}} \quad (3)$$

329 where $X = \{X_0, X_1, \dots, X_{n-1}\}$ and $Y = \{Y_0, Y_1, \dots, Y_{n-1}\}$ are the features vectors extracted from images
 330 acquired at different conditions or different delineations.

331 Experiments

332 Experiments were designed following a similar approach to the IQT one.²⁶ First, the
 333 controlled sample set was used to determine reference values for comparison purposes when
 334 using Correlation and Chebyshev distance. Concretely, the best three methods were selected
 335 and then reference values for Correlation and Chebyshev distances were determined. Once
 336 methods were selected, we evaluated the robustness of the selected methods using the clinical
 337 sample set by comparing the results with the measures previously obtained. A summary of the
 338 experiments, including number of images for both sample sets, is displayed in **Figure 6**. The
 339 texture-based methods (GLCM, LBP, HOG LPQ and riLPQ) were ranked according to the
 340 robustness assessed (1) with the controlled sample set. Then, only those methods that
 341 presented better robustness were validated (2) with the clinically acquired ultrasound images.
 342 The experiments are explained in more detail below.

343 *Texture-based methods ranking using the controlled sample set*

344 For each texture and texture-analysis method the similarity measures (Correlation and
345 Chebyshev distances) were computed using the controlled databases (OUTEX and PHOTEX).
346 Robustness for each acquisition parameter was assessed, the parameter of interest was not
347 fixed to any value while the rest of the acquisition parameters were fixed resulting in different
348 acquisition scenarios. Then, both similarity measures were computed between the different
349 textural features of the same texture acquired at different settings of the same parameter of
350 interest. In this manner, the robustness for each acquisition parameter was isolated. This
351 procedure was repeated for each parameter of interest till all the acquisition parameters were
352 unfixed once. Finally, to summarize the robustness for each acquisition parameter and texture
353 mean and standard deviation were computed over fixed parameters (different scenarios) for
354 each similarity measurement resulting in a unique value [mean±std]. For instance, to assess
355 illumination robustness using OUTEX database samples (illumination had 'horizon', 'inca' and
356 'TL84' labels), resolution and rotation were fixed resulting in a total of 54 scenarios (6 resolution
357 levels and 9 rotation degrees) for each texture (**Figure 7**). Then, mean and standard deviation
358 were computed for each similarity measurement over the 54 scenarios. In this example, a total
359 of 3 similarity values [mean±std] from 2 similarity measures for 3 different labels were obtained
360 for each texture. In order to compare robustness of the texture-based methods for each
361 acquisition parameter, for each similarity measure the mean among similarity values was
362 computed for each texture and then among all textures. In this manner, a unique value for each
363 similarity measure, acquisition parameter, database (OUTEX and PHOTEX) and texture-based
364 method was obtained.

365 The same approach was used to assess robustness regarding the different delineations;
366 similarity measures were computed for the overlapped but different size ROIs and the non-
367 overlapped ROIs delineated in the same texture image. Mean and standard deviation were
368 computed over overlapped and non-overlapped delineations for each similarity measure
369 resulting in a unique value for each texture image. Then, robustness for non-overlapped and

370 overlapped delineations was compared between the different texture-based methods
371 computing the mean among similarity values [mean±std] for each similarity measure and each
372 texture, and then among all selected textures. A unique similarity value was obtained for each
373 similarity measure, the non-overlapped and overlapped delineations, each database and
374 texture-based method.

375 Those texture-based methods that presented lower similarity values in regards of
376 acquisition parameters and delineations were considered the most robust methods. Based on
377 this criterion, methods were ranked from the most to the least robust in relation to acquisitions
378 and delineations for each database (OUTEX and PHOTEX) first. Then, each texture-based method
379 was globally ranked according to the number of times it ranked the best. The first three methods
380 were elected for validation using clinical images.

381 *Validation of the robust methods using the clinically acquired ultrasound images*

382 Robustness of those methods that obtained better results using the controlled sample
383 set was validated using fetal lung ultrasound images. Different experiments were performed as
384 detailed below.

385 First, we assumed that left and right lungs of the same patient have the same type of
386 tissue and in consequence images of both lungs acquired at different conditions should show
387 the same or similar textural features. Based on this, robustness for illumination, resolution and
388 rotation was indirectly validated by computing similarity measurements between proximal and
389 distal lungs that were at different depth positions. Different illumination and resolution
390 conditions of the same tissue were indirectly achieved since lateral speckle size is strongly
391 dependent on the depth within the tissue and acoustic attenuation is dependent on depth.^{5,40}
392 Robustness for rotation was also assessed using the fetal lung ultrasound images acquired with
393 different fetal spine orientations. In this manner, the same ultrasound tissue at different
394 rotation conditions (with respect to proximal and distal lungs) was achieved. For each texture-

395 based method, mean and standard deviation of the Correlation and Chebyshev distances were
396 computed among ultrasound fetal lung images for manual and semiautomatic delineations.

397 Second, in order to validate the robustness dependence of the selected texture-based
398 methods to ultrasound systems, robustness results for illumination, resolution and rotation
399 were stratified for the different ultrasound systems brands used in our clinical setting. No
400 dependence to systems was considered when similar robustness was obtained between
401 ultrasound systems of different brands. ANOVA was computed over the stratified values
402 (Siemens, General Electrics, Toshiba and Aloka).

403 Finally, robustness for different delineations was assessed for each texture-based
404 method. Similarity measurements were computed between the eroded ROIs from the manual
405 and semiautomatic delineations. Mean and standard deviation of the similarities were
406 computed among all the proximal and distal lungs for each method and the manual and
407 semiautomatic delineations.

408 All computations in this study were performed using MATLAB R2014b (version
409 8.4.0.150421; MATLAB; The MathWorks Inc., Natick, Mass., USA).

410

411

412

413

414

415

416

417

418

419

420

421

422

423 **Results**

424 *Selection of non-ultrasound images (Controlled data set)*

425 No significant differences were shown between the mean, skewness and kurtosis of the
426 histograms computed from the non-ultrasound selected images and the histograms computed
427 from the fetal lung ultrasound textures.

428 *Texture-based methods ranking*

429 Similarity results will be presented in the form of mean (with standard deviation (SD) of).
430 Similarity results between features extracted from each texture acquired at different
431 illumination, resolution and rotation labels are given in **Table 1**. Regarding OUTEX database,
432 most methods showed high robustness when illumination acquisition parameter was left free
433 ('horizon', 'inca' and 'TL84'). For illumination in PHOTEX database, GLCM, LBP and riLPQ texture-
434 based methods presented more robustness in comparison with the rest of the methods (HOG
435 and LPQ). Specifically, HOG and LPQ method resulted in a correlation distance of 0.36 (0.15) and
436 0.29 (0.16 SD), respectively. GLCM, LBP and riLPQ were the most robust methods for resolution
437 and rotation parameters stratified in OUTEX database while HOG and LPQ methods performed
438 poorly for these parameters. HOG and LPQ methods presented less robustness for rotation in
439 PHOTEX database than the other methods as well.

440 Similarity results for different delineations in the OUTEX and PHOTEX databases are
441 displayed in **Table 2**. HOG and LPQ methods resulted the worst in terms of robustness for
442 different delineations using both databases. Maximum similarity values between textural
443 features extracted by HOG and LPQ in different overlapped ROIs were 0.32 (0.13) and 0.42 (0.21),
444 respectively, and 0.27 (0.13) and 0.42 (0.30) for the non-overlapped ones. On the other hand,
445 LBP and riLPQ performed better for the non-overlapped delineations than the other methods.

446 Overall, robustness performance for GLCM, LPB and riLPQ texture-based methods
447 resulted favorably when compared with HOG and LPQ. In fact, these methods showed similarity

448 values close to 0 for the acquisition variations in almost all acquisition parameters and
449 delineation from both controlled databases (OUTEX and PHOTEX). **Table 3** shows the ranking of
450 the robustness of the texture-based methods in relation to acquisition conditions and
451 delineations for each Data Set.

452 *Validation of the robust methods*

453 **Table 4** displays similarity results between proximal and distal lungs of all images.
454 Overall results confirmed robustness for all the evaluated methods (LBP, riLPQ and GLCM)
455 depending on the similarity measure and the two operator dependent delineations (manual and
456 semiautomatic). The highest similarity was shown for the riLPQ method using the manual
457 delineation but overall the LBP method performed the best. The GLCM resulted in the worst
458 method in terms of robustness when using semiautomatic delineations and measuring
459 Correlation distance although Chebyshev distance resulted close to 0.

460 Stratified results by ultrasound brand are shown in **Table 4**. A total of 198, 392, 56 and
461 20 fetal lung ultrasound images were acquired using Siemens, General Electrics, Toshiba and
462 Aloka ultrasound systems, respectively. Similar results were shown when comparing robustness
463 stratified by ultrasound brands. Results demonstrated that variations in indirect illumination,
464 resolution and rotation were not dependent on the ultrasound system. No significant
465 differences ($p>0.05$) were found for the GLCM, LBP and riLPQ texture-based methods after
466 stratifying by ultrasound brands.

467 Similarity results between textural features extracted from different ROIs are displayed
468 in Table 5. Mean similarity values were computed among all proximal and distal lungs. Results
469 confirmed robustness for delineations for all selected methods evaluated in the controlled
470 setting (LBP, riLPQ and GLCM).

471 **Discussion**

472 This study provides evidence that texture analysis can be used to extract robust
473 information from ultrasound images acquired under different conditions. This supports the use
474 of texture analysis to obtain reliable features from ultrasound images, which is required to use
475 those features for clinical purposes in a classification or grading systems.

476 Different quantitative ultrasound-based techniques have been explored to extract
477 information from the signals causing speckle that are associated to the underlying tissue
478 microstructure.^{15,16} These techniques have shown promising results such as transient
479 elastography for the staging of liver fibrosis,⁴¹ spectral-based quantitative ultrasound
480 parameters to characterize breast cancer and detect response of breast cancer to
481 therapy^{42,43} and most recently shear wave elasticity imaging for the assessment of cervical
482 softening⁴⁴. Some of these techniques are implemented on specific devices and have
483 demonstrated to be invariant to different operators and systems.¹⁶ Despite this, some of them
484 have not been capable of detecting specific pathologies that still being prevalent in general
485 population. Perhaps, because its approaches are inadequate and are not able to obtain relevant
486 information from any tissue. Quantitative ultrasound texture analysis might become a new
487 clinical tool that might provide new insight for clinical diagnosis.

488 Several attempts have been made to obtain clinical information related to a
489 pathophysiological process using quantitative ultrasound texture analysis in a robust way.
490 Oosterveld et al.²⁰ analyzed the texture of B-mode images to differentiate diffuse liver diseases
491 and evaluated its reproducibility over a 5 days period. In that study, the B-mode images were
492 reconstructed by radiofrequency signals that were corrected by attenuation to remove the
493 depth. Results showed the possibility to correct the depth dependencies of the B-mode texture.
494 Garra et al.¹⁹ used quantitative analysis of ultrasound image texture to distinguish benign from
495 malignant breast lesions showing promising results. Nonetheless, Garra et al.¹⁹ concluded that
496 the method presented ultrasound system dependence. Previous methodologies showed

497 promising results but not its feasibility for clinical practice. Other studies demonstrated a high
498 diagnostic accuracy for detection of subtle changes in affected tissues non-visible for the human
499 eye. However, no perspective studies have been conducted to validate its robustness in a clinical
500 setting.

501 To our knowledge, this is the first study reporting accurate robustness of quantitative
502 ultrasound texture analysis considering only the specific textural features and not the prediction
503 rate for a clinical event, using machine learning algorithms. The main difference between this
504 study and the previous ones is that robustness of ultrasound texture features was assessed using
505 a large number of controlled (non-medical) images. The data sets used in this study emulate
506 ultrasound acquisition conditions, which are usually present in a clinical setting. Additionally,
507 several ROIs were performed to assess robustness when delineating. Our study shows that the
508 LBP, riLPQ and GLCM methods were the three most robust methods for extracting information
509 from images acquired under different conditions and different delineations in the controlled
510 setting (**Table 1, 2 and 3**). It should be noticed that LBP and riLPQ methods were the most robust
511 in both databases (OUTEX and PHOTEX). These methods have not been widely used for
512 ultrasound texture classification in literature. Thus, this finding opens the possibility to explore
513 new methods to develop ultrasound texture-based tools. Then, the most robust methods (LBP,
514 riLPQ and GLCM) were validated using clinically acquired ultrasound images acquired by several
515 ultrasound machines and operators. Our results validated robustness in relation to acquisition
516 conditions using LBP, riLPQ and GLCM and showed to be invariant against ultrasound machines
517 (**Table 4**). Concretely, LBP performed the best; the riLPQ and GLCM methods presented low
518 similarity values in relation to acquisitions according to the delineation mode (manual or
519 semiautomatic) and the similarity measure (Correlation and Chebyshev). Robustness against
520 multiple delineations was also validated using clinically acquired ultrasound images. All methods
521 resulted in low similarity values according to the delineation mode or the similarity measure

522 (Table 5). These results confirm that a texture-based tool that integrates a classification system
523 could be developed using any of the tested methods.

524 Even though three of all the texture-based methods, LBP, riLPQ and GLCM showed
525 robustness using clinically acquired ultrasound images, the use of these methods to develop a
526 clinical tool needs to be demonstrated. Our results do not evidence the suitability of these
527 methods to assess pathophysiological conditions involved in most of the tissues, it will depend
528 on the intrinsic properties of textural features extracted by each texture analysis method. In fact,
529 a method that always gives the same values will be the most robust method but completely
530 useless. Additionally, robustness was assessed in the controlled setting over all acquisition
531 conditions discretely and not considering specific ranges. In some cases, depending on the organ
532 to be scanned (i.e. carotid artery or fetal heart), acquisition protocols might include repeatable
533 acquisitions with acquisition parameters fixed within particular ranges. Therefore, the discarded
534 texture-based methods might obtain repeatable features within specific ranges and provide
535 useful information related to the underlying pathophysiological process. Moreover, it should be
536 noticed that robustness was validated comparing proximal versus distal lungs. Robustness of the
537 methods that presented higher similarities when comparing both fetal lungs would be improved
538 using a focal configuration and evaluating tissues within the same depth. Hence, when exploring
539 texture ultrasound analysis to develop a clinical tool, an acquisition protocol should be designed
540 to obtain the most repeatable acquisitions.

541 The main strength of our study is that feasibility of texture analysis to obtain ultrasound
542 features in a robust way was tested using non-ultrasound images acquired under controlled
543 conditions similar to ultrasound and clinically acquired fetal lung ultrasound images. On the one
544 hand, the non-ultrasound set provides different images of the same tissue acquired in a very
545 precise way in contrast to whichever ultrasound setting that depends on the ability of the
546 radiologist. This opens the possibility to evaluate a higher number of images of the same texture
547 acquired under different conditions than in the theoretical case of evaluating real ultrasound

548 images. Furthermore, images were acquired combining parameters with the whole range, thus
549 emulating possible acquisition conditions of whichever ultrasound setting where textures are
550 scanned from any organ. On the other hand, testing ultrasound texture-based methods
551 robustness using fetal lung ultrasound images expands opportunities to explore the same
552 methods for quantifying textural changes in other organs, even in adult scans where acquisition
553 conditions might be more repeatable. Another strength of our study is the use of the fetal lung
554 ultrasound images to compare the same lung tissue at different depths (proximal and distal fetal
555 lungs). Our results represent a forward step in relation to the study published by Thijssen²⁵.
556 Thijssen²⁵ suggested that texture analysis based on second order statistics should be used in the
557 axial direction exclusively since speckle size changes according to depth and attenuation strongly.
558 Finally, several ultrasound systems were used to acquire our clinical images. Speckle patterns
559 might be related to system since wave propagation fundamentals, such as wavelength or gain,
560 are post-processed in the system. In our study, we demonstrated that it is possible to configure
561 similar settings in different ultrasound systems without affecting robustness of the selected
562 methods (LBP, riLPQ and GLCM).

563 This study has some limitations that should be acknowledged. First, non-controlled
564 resolution images in PHOTEX database might affect robustness evaluation between non-
565 overlapped delineations. We believe that non-overlapped ROIs (of the same image) present
566 different textural content between them when the resolution is high. For instance, the GLCM
567 method resulted in a high dissimilarity (Correlation distance) only for non-overlapped
568 delineations in PHOTEX database (**Table 2**) where resolution was not controlled. Second, we
569 used clinically acquired ultrasound images of the fetal lungs to validate the robustness of the
570 selected texture-based methods, but only robustness for different lungs (proximal versus distal)
571 and delineations of the same tissue were assessed. In fact, for this study we assumed that
572 proximal and distal lungs of the same patient present the same tissue without being previously
573 demonstrated in the literature. Ideally, the robustness evaluation should be performed using

574 different controlled acquisitions of the same organ and patient. Although different ultrasound
575 images of a same patient were acquired in some cases, acquisition conditions were similar since
576 they were acquired for clinical purposes using a similar setting. To evaluate robustness for
577 ultrasound images acquired under different conditions in a controlled way, a robustness study
578 using different ultrasound images of the same tissue (i.e. from carotid artery or liver in adults)
579 should be performed. Third, this study evaluated the repeatability of specific textural features
580 obtained from images acquired under different conditions and different delineations without
581 demonstrating its ability to detect differences against a clinical outcome of interest. We
582 acknowledge that an additional study to compare the prediction of a clinical outcome with the
583 same ultrasound tissue acquired at different conditions should be performed. Nonetheless, the
584 use of texture analysis to develop a robust clinical tool has been recently demonstrated by
585 Palacio et al.⁴⁵ In that study, a prospective multicenter study in 20 centers worldwide was
586 undergone including a total of 730 samples for the final analysis, different operators and
587 different ultrasound systems. The results showed that quantitative ultrasound of fetal lung
588 texture predicted neonatal respiratory morbidity with a sensitivity, specificity, positive
589 predictive value and negative predictive value of 74.3%, 88.6%, 51.6% and 95.5%, respectively.
590 These promising results support our findings, suggesting that texture analysis may provide
591 robust and relevant information useful for clinical diagnosis.

592 In summary, this study provides evidence that ultrasound tissues can be characterized
593 by quantitative texture analysis in a robust way allowing its use for diagnostic purpose in clinical
594 practice. These results should be confirmed in larger clinical images of the same tissue acquired
595 under different controlled conditions and validated using this information to examine the ability
596 to detect differences against a clinical outcome in a reliable manner.

597

598 **Supplementary material**

599 An example of the selection of the non-ultrasound images and histograms is shown in

600 **Figure S.1.**

601 The distribution of the resolution and rotation angle of the fetal lung ultrasound images

602 used for this study is displayed in **Figure S.2** and **Figure S.3**, respectively.

603 A summary table of the texture-based methods used for this study is shown in **Table S.1.**

604

605 **ACKNOWLEDGEMENTS**

606 This work was partially supported by grants from “la Secretaria d’Universitats I Recerca
607 del Departament d’Economia i Coneixement de la Generalitat de Catalunya (A.P: 2014DI083)”,
608 The Cerebra Foundation for the Brain Injured Child (Carmarthen, Wales, UK) and Obra Social “la
609 Caixa”. Additionally, this publication has been funded with support of the Erasmus + Programme
610 of the European Union (Framework Agreement number: 2013-0040). This publication reflects
611 the views only of the author, and the Commission cannot be held responsible for any use which
612 may be made of the information contained therein.

613 **REFERENCES**

- 614 1. Castellano G, Bonilha L, Li LM, Cendes F. Textures analysis of medical images. Clin Radiol
615 2004; 59:1061-9.
- 616 2. Haralick RM, Shanmugam K. Textural Features for Image Classification. IEEE Trans Syst
617 Man, Cybern, Syst 1973; 3:610-21.
- 618 3. Junior OL, Delgado D, Gonçalves V, Nunes U. Trainable classifier-fusion schemes: An
619 application to pedestrian detection. In Intelligent Transportation Systems, 2009. ITSC'09.
620 12th International IEEE Conference on 2009 Oct 4 (pp. 1-6). IEEE.
- 621 4. Ojala T, Pietikainen M, Maenpaa T. Multiresolution gray-scale and rotation invariant
622 texture classification with local binary patterns. IEEE Trans Pattern Anal Mach Intell 2002;
623 24:971-87.
- 624 5. Oosterveld BJ, Thijssen JM, Verhoef WA. Texture of B-mode echograms: 3-D simulations
625 and experiments of the effects of diffraction and scatterer density. Ultrason Imaging
626 1985; 7:142-60.
- 627 6. Bergen JR, Adelson EH. Theories of visual texture perception. Spat Vision 1991; 10:114-
628 34.
- 629 7. Insana MF, Garra BS, Rosenthal SJ, Hall TJ. Quantitative ultrasonography. Med Prog
630 Technol 1988; 15:141-153.
- 631 8. Tunis AS, Czarnota GJ, Giles A, Sherar MD, Hunt JW, Kolios MC. Monitoring structural
632 changes in cells with high-frequency ultrasound signal statistics. Ultrasound Med Biol
633 2005; 31:1041-9.
- 634 9. Bonet-Carne E, Palacio M, Cobo T, et al. Quantitative ultrasound texture analysis of fetal
635 lungs to predict neonatal respiratory morbidity. Ultrasound Obstet Gynecol 2015;
636 45:427-33.

- 637 10. Chen DR, Chang RF, Kuo WJ, Chen MC, Huang YL. Diagnosis of breast tumors with
638 sonographic texture analysis using wavelet transform and neural networks. *Ultrasound*
639 *Med Biol* 2002; 28:1301-10.
- 640 11. Hartman PC, Oosterveld BJ, Thijssen JM, Rosenbusch GJ. Variability of quantitative
641 echographic parameters of the liver: intra- and interindividual spread, temporal- and
642 age- related effects. *Ultrasound Med Biol* 1991; 17:857-67.
- 643 12. Tenorio V, Bonet-Carne E, Figueras F, et al. Correlation of quantitative texture analysis
644 of cranial ultrasound with later neurobehavior in preterm infants. *Ultrasound Med Biol*
645 2014; 40:2285-94.
- 646 13. Sujana H, Swarnamani S, Suresh S. Application of artificial neural networks for the
647 classification of liver lesions by image texture parameters. *Ultrasound Med Biol* 1996;
648 22:1177-81.
- 649 14. Vince DG, Dixon KJ, Cothren RM, Cornhill JF. Comparison of texture analysis methods for
650 the characterization of coronary plaques in intravascular ultrasound images. *Comput*
651 *Med Imaging Graph* 2000; 24:221-9.
- 652 15. Oelze ML. Emerging quantitative ultrasound applications: From diagnosing disease to
653 monitoring of therapy. *The Journal of the Acoustical Society of America*. 2016
654 Oct;140(4):3136-.
- 655 16. Oelze ML, Mamou J. Review of quantitative ultrasound: Envelope statistics and
656 backscatter coefficient imaging and contributions to diagnostic ultrasound. *IEEE*
657 *transactions on ultrasonics, ferroelectrics, and frequency control*. 2016 Feb;63(2):336-
658 51.
- 659 17. Christodoulou CI, Pattichis CS, Pantziaris M, Nicolaidis A. Texture-based classification of
660 atherosclerotic carotid plaques. *IEEE Trans Med Imaging* 2003; 22:902-12.
- 661 18. El-Gayar MM, Soliman H. A comparative study of image low level feature extraction
662 algorithms. *Egyptian informatics Journal* 2013; 14:175-81.

- 663 19. Garra BS, Krasner BH, Horii SC, Ascher S, Mun SK, Zeman RK. Improving the distinction
664 between benign and malignant breast lesions: the value of sonographic texture analysis.
665 Ultrason Imaging 1993; 15:267-85.
- 666 20. Oosterveld BJ, Thijssen JM, Hartman PC, Romijn RL, Rosenbusch GJ. Ultrasound
667 attenuation and texture analysis of diffuse liver disease: methods and preliminary
668 results. Phys Med Biol 1991; 36:1039.
- 669 21. Schmitz G, Ermert H, Senge T. Tissue-characterization of the prostate using radio
670 frequency ultrasonic signals. IEEE Trans Ultrason Ferroelectr Freq Control 1999; 46:126-
671 38.
- 672 22. Serizawa M, Maeda K. Noninvasive fetal lung maturity prediction based on gray level
673 histogram width. Ultrasound Med Biol 2010; 36:1998-2003.
- 674 23. Ojansivu V, Heikkilä J. Blur insensitive texture classification using local phase
675 quantization. In International conference on image and signal processing 2008 Jul 1 (pp.
676 236-243). Springer Berlin Heidelberg.
- 677 24. Ojansivu V, Rahtu E, Heikkila J. Rotation invariant local phase quantization for blur
678 insensitive texture analysis. In Pattern Recognition, 2008. ICPR 2008. 19th International
679 Conference on 2008 Dec 8 (pp. 1-4). IEEE.
- 680 25. Thijssen JM. Ultrasonic speckle formation, analysis and processing applied to tissue
681 characterization. Pattern Recognit Lett 2003; 24:659-75.
- 682 26. Alexander DC, Zikic D, Zhang J, Zhang H, Criminisi A. Image quality transfer via random
683 forest regression: applications in diffusion MRI. In International Conference on Medical
684 Image Computing and Computer-Assisted Intervention 2014 Sep 14 (pp. 225-232).
685 Springer, Cham.
- 686 27. Hossain S, Serikawa S. Texture databases-a comprehensive survey. Pattern Recognit Lett
687 2013; 34:2007-22.

- 688 28. Ojala T, Maenpaa T, Pietikainen M, Viertola J, Kyllonen J, Huovinen S. Outex-new
689 framework for empirical evaluation of texture analysis algorithms. In Pattern
690 Recognition, 2002. Proceedings. 16th International Conference on 2002 (Vol. 1, pp. 701-
691 706). IEEE.
- 692 29. Targhi AT, Geusebroek JM, Zisserman A. Texture classification with minimal training
693 images. In Pattern Recognition, 2008. ICPR 2008. 19th International Conference on 2008
694 Dec 8 (pp. 1-4). IEEE.
- 695 30. Giesen RJ, Huynen AL, Aarnink RG, de la Rosette JJ, Debruyne FM, Wijkstra H.
696 Construction and application of hierarchical decision tree for classification of
697 ultrasonographic prostate images. *Med Biol Eng Comput* 1996; 34:105-9.
- 698 31. Poonguzhali S, Ravindran G. Automatic classification of focal lesions in ultrasound liver
699 images using combined texture features. *Information Technology Journal* 2008; 7:205-
700 9.
- 701 32. Baños N, Perez-Moreno A, Migliorelli F, et al. Quantitative analysis of the cervical texture
702 by ultrasound and correlation with gestational age. *Fetal Diagn Ther* 2017; 41:265-72.
- 703 33. Keramidas EG, Iakovidis DK, Maroulis D, Dimitropoulos N. Thyroid texture
704 representation via noise resistant image features. In *Computer-Based Medical Systems,*
705 2008. CBMS'08. 21st IEEE International Symposium on 2008 Jun 17 (560-565). IEEE.
- 706 34. Nanni L, Lumini A, Brahnam S. Local binary patterns variants as texture descriptors for
707 medical image analysis. *Artif Intell Med* 2010; 49:117-25.
- 708 35. Beyerer J, León FP, Frese C. *Machine vision: Automated visual inspection: Theory,*
709 *practice and applications.* Springer, 2015 Oct. 1
- 710 36. Pazinato DV, Stein BV, de Almeida WR, et al. Pixel-level tissue classification for
711 ultrasound images. *IEEE J Biomed Health Inform* 2016; 20:256-67.

- 712 37. Ravishankar H, Annangi P, Washburn M, Lanning J. Automated kidney morphology
713 measurements from ultrasound images using texture and edge analysis. In SPIE Medical
714 Imaging 2016 Apr 1 (pp. 97901A-97901A). International Society for Optics and Photonics.
- 715 38. Deng Y, Wang Y, Chen P, Yu J. A hierarchical model for automatic nuchal translucency
716 detection from ultrasound images. *Comput Biol Med* 2012; 42:706-13.
- 717 39. Tenbrinck D, Schmid S, Jiang X, Schäfers K, Stypmann J. Histogram-based optical flow for
718 motion estimation in ultrasound imaging. *J Math Imaging Vis* 2013; 47:138-50.
- 719 40. Huisman HJ, Thijssen JH. An in vivo ultrasonic model of liver parenchyma. *IEEE Trans*
720 *Ultrason Ferroelectr Freq Control* 1998; 45:739-50.
- 721 41. Friedrich–Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, Herrmann E.
722 Performance of transient elastography for the staging of liver fibrosis: a meta-analysis.
723 *Gastroenterology*. 2008 Apr 1;134(4):960-74.
- 724 42. Sadeghi-Naini A, Papanicolau N, Falou O, Zubovits J, Dent R, Verma S, Trudeau M,
725 Boileau JF, Spayne J, Iradji S, Sofroni E. Quantitative ultrasound evaluation of tumor cell
726 death response in locally advanced breast cancer patients receiving chemotherapy.
727 *Clinical Cancer Research*. 2013 Feb 20.
- 728 43. Sannachi L, Tadayyon H, Sadeghi-Naini A, Tran W, Gandhi S, Wright F, Oelze M, Czarnota
729 G. Non-invasive evaluation of breast cancer response to chemotherapy using
730 quantitative ultrasonic backscatter parameters. *Medical image analysis*. 2015 Feb
731 1;20(1):224-36.
- 732 44. Rosado-Mendez IM, Carlson LC, Woo KM, Santoso AP, Guerrero QW, Palmeri ML,
733 Feltovich H, Hall TJ. Quantitative assessment of cervical softening during pregnancy in
734 the Rhesus macaque with shear wave elasticity imaging. *Physics in Medicine & Biology*.
735 2018 Apr 19;63(8):085016.

736 45. Palacio M, Bonet-Carne E, Cobo T, et al. Prediction of neonatal respiratory morbidity by
737 quantitative ultrasound lung texture analysis: a multicenter study. American Journal of
738 Obstetrics and Gynecology. 2017 Mar 23.
739

740 **TABLES**

741 **Table 1.** Similarity results for images acquired under different conditions in the controlled
 742 setting. Lower distance (values close to 0) indicates similarity (robustness); higher distance
 743 (values close to 1) indicates dissimilarity.

Database	Methods	Illumination		Resolution		Rotation	
		Corr	Cheb	Corr	Cheb	Corr	Cheb
OUTEX	GLCM	0.05 (0.02)	0.17 (0.03)	0.01 (0.01)	0.06 (0.03)	0.00 (0.00)	0.02 (0.01)
	LBP	0.02 (0.01)	0.07 (0.02)	0.06 (0.02)	0.11 (0.02)	0.00 (0.00)	0.02 (0.01)
	HOG	0.04 (0.03)	0.05 (0.02)	0.15 (0.06)	0.11 (0.02)	0.39 (0.11)	0.17 (0.04)
	LPQ	0.04 (0.03)	0.02 (0.01)	0.21 (0.09)	0.04 (0.01)	0.20 (0.11)	0.04 (0.02)
	riLPQ	0.01 (0.01)	0.01 (0.00)	0.07 (0.01)	0.03 (0.01)	0.01 (0.01)	0.01 (0.01)
PHOTEX	GLCM	0.01 (0.01)	0.13 (0.10)	-	-	0.03 (0.01)	0.15 (0.05)
	LBP	0.01 (0.01)	0.02 (0.01)	-	-	0.02 (0.01)	0.11 (0.02)
	HOG	0.36 (0.15)	0.23 (0.11)	-	-	0.37 (0.11)	0.36 (0.06)
	LPQ	0.29 (0.16)	0.04 (0.02)	-	-	0.43 (0.07)	0.10 (0.02)
	riLPQ	0.03 (0.02)	0.03 (0.01)	-	-	0.17 (0.05)	0.06 (0.02)

744 Data is given as mean (SD). Corr, Correlation distance. Cheb, Chebyshev distance. GLCM, Gray-
 745 Level Co-occurrence Matrices. LBP, Low Binary Patterns. HOG, Histogram of Oriented Gradients.
 746 LPQ, Local Phase Quantization. riLPQ, rotation invariant Local Phase Quantization.

747

748

749

750

751

752

753

754

755

756

757

758 **Table 2.** Similarity results for different delineations in the controlled setting. Lower distance
 759 (values close to 0) indicates similarity (robustness); higher distance (values close to 1) indicates
 760 dissimilarity.

Database	Methods	Overlapped		Non-overlapped	
		Corr	Cheb	Corr	Cheb
OUTEX	GLCM	0.02 (0.05)	0.01 (0.00)	0.05 (0.11)	0.01 (0.01)
	LBP	0.02 (0.03)	0.06 (0.04)	0.02 (0.03)	0.06 (0.05)
	HOG	0.18 (0.15)	0.32 (0.13)	0.19 (0.17)	0.27 (0.13)
	LPQ	0.25 (0.11)	0.06 (0.03)	0.17 (0.15)	0.04 (0.04)
	riLPQ	0.10 (0.04)	0.04 (0.02)	0.03 (0.04)	0.02 (0.01)
PHOTEX	GLCM	0.01 (0.04)	0.01 (0.00)	0.21 (0.30)	0.03 (0.03)
	LBP	0.01 (0.02)	0.03 (0.02)	0.02 (0.06)	0.03 (0.03)
	HOG	0.13 (0.17)	0.31 (0.15)	0.12 (0.13)	0.23 (0.13)
	LPQ	0.42 (0.21)	0.04 (0.02)	0.42 (0.30)	0.03 (0.02)
	riLPQ	0.09 (0.05)	0.05 (0.03)	0.04 (0.05)	0.04 (0.02)

761 Data is given as mean (SD). Corr, Correlation distance. Cheb, Chebyshev distance. GLCM, Gray-
 762 Level Co-occurrence Matrices. LBP, Low Binary Patterns. HOG, Histogram of Oriented Gradients.
 763 LPQ, Local Phase Quantization. riLPQ, rotation invariant Local Phase Quantization.

764
 765
 766
 767
 768
 769
 770
 771
 772
 773
 774

775 **Table 3.** Ranking of the texture-based methods robustness. Methods are ranked from the most
 776 (1) to the least (5) robust in relation to acquisitions and delineations for each database (OUTEX
 777 and PHOTEX).

Methods	General ranking	AcquisitionConditions		Delineations	
		OUTEX	PHOTEX	OUTEX	PHOTEX
LBP	1	2	1	2	1
riLPQ	2	1	2	3	2
GLCM	3	3	3	1	3
LPQ	4	4	4	4	5
HOG	5	5	5	5	4

778 GLCM, Gray-Level Co-occurrence Matrices. LBP, Low Binary Patterns. HOG, Histogram of
 779 Oriented Gradients. LPQ, Local Phase Quantization. riLPQ, rotation invariant Local Phase
 780 Quantization.

781

782

783

784

785

786

787

788

789

790

791

792

793

794

795

796 **Table 4.** Similarity results for proximal and distal fetal lungs in the clinical ultrasound set. Lower
 797 distance (values close to 0) indicates similarity (robustness); higher distance (values close to 1)
 798 indicates dissimilarity.

Methods	US brand	Manual		Semiautomatic		<i>p value</i>
		Corr	Cheb	Corr	Cheb	
LBP	All	0.05 (0.04)	0.13 (0.10)	0.07 (0.06)	0.04 (0.04)	0.5971
	Siemens	0.04 (0.03)	0.11 (0.09)	0.05 (0.04)	0.04 (0.04)	
	GE	0.06 (0.05)	0.15 (0.11)	0.08 (0.06)	0.04 (0.04)	
	Toshiba	0.08 (0.05)	0.07 (0.04)	0.09 (0.05)	0.02 (0.02)	
	Aloka	0.06 (0.05)	0.04 (0.02)	0.08 (0.07)	0.01 (0.01)	
riLPQ	All	0.00 (0.00)	0.14 (0.11)	0.17 (0.23)	0.23 (0.18)	0.9956
	Siemens	0.00 (0.01)	0.16 (0.12)	0.12 (0.21)	0.22 (0.16)	
	GE	0.00 (0.00)	0.13 (0.11)	0.20 (0.25)	0.24 (0.19)	
	Toshiba	0.00 (0.00)	0.11 (0.10)	0.17 (0.22)	0.23 (0.17)	
	Aloka	0.00 (0.00)	0.22 (0.14)	0.06 (0.14)	0.27 (0.22)	
GLCM	All	0.16 (0.14)	0.14 (0.10)	0.51 (0.31)	0.04 (0.03)	0.9656
	Siemens	0.12 (0.12)	0.14 (0.12)	0.36 (0.27)	0.04 (0.03)	
	GE	0.19 (0.14)	0.15 (0.10)	0.59 (0.30)	0.04 (0.03)	
	Toshiba	0.13 (0.11)	0.09 (0.04)	0.44 (0.29)	0.03 (0.01)	
	Aloka	0.19 (0.11)	0.05 (0.04)	0.48 (0.28)	0.02 (0.01)	

799 Data is given as mean (SD). The results for all images are in bold. Corr, Correlation distance. Cheb,
 800 Chebyshev distance. GLCM, Gray-Level Co-occurrence Matrices. LBP, Low Binary Patterns. HOG,
 801 Histogram of Oriented Gradients. LPQ, Local Phase Quantization. riLPQ, rotation invariant Local
 802 Phase Quantization.

803
 804
 805
 806
 807
 808
 809

810 **Table 5.** Similarity results for different delineations in the clinical ultrasound set. Lower distance
 811 (values close to 0) indicates similarity (robustness); higher distance (values close to 1) indicates
 812 dissimilarity.

Methods	Manual		Semiautomatic	
	Corr	Cheb	Corr	Cheb
LBP	0.08 (0.05)	0.05 (0.01)	0.23 (0.09)	0.02 (0.00)
riLPQ	0.00 (0.00)	0.15 (0.08)	0.02 (0.03)	0.23 (0.11)
GLCM	0.03 (0.04)	0.05 (0.01)	0.12 (0.09)	0.01 (0.00)

813 Data are given as mean (SD). Corr, Correlation distance. Cheb, Chebyshev distance. GLCM, Gray-
 814 Level Co-occurrence Matrices. LBP, Low Binary Patterns. HOG, Histogram of Oriented Gradients.
 815 LPQ, Local Phase Quantization. riLPQ, rotation invariant Local Phase Quantization.

816

817

818

819

820

821

822

823

824

825

826

827 **Table S.1.** Summary of the texture-based methods.

Summary of the methods					
Acronym	Name	Basis	Parameters	Features Number	Reference
GLCM	Gray-Level Co-occurrence Matrices	Co-occurrence Matrix	Adjacency direction = 0 Gray levels = 8	64	Haralick et al.
LBP	Local Binary Patterns	Uniform patterns	Radius (R) = 1 Number of neighbors (P) = 16	18	Ojala et al.
HOG	Histogram of Oriented Gradients	Gradient orientation values frequencies	Number of cells = 3x3 Number of histogram bins = 9	81	Junior et al.
LPQ	Local Phase Quantization	Short Term Fourier Transform	Window size = 9x9	256	Garra et al.
riLPQ	rotation invariant LPQ	Compensates image rotation considering direction of local phase characterization	Window size = 9x9 Number of angles = 36	256	Oosterveld et al.

828

829

830

831

832

833

834

835

836

837

838

839 **FIGURE LEGENDS**

840 **Figure 1.** Example of a selected (a) and a non-selected (b) texture image for the controlled Data
841 Set.

842 **Figure 2.** Non-overlapped regions of interest (ROIs) divisions (dotted lines) of a texture image in
843 the controlled setting (texture from PHOTEX database). The original image is divided into 25
844 different ROIs.

845 **Figure 3.** 28 Overlapped (with different sizes) ROIs of a texture image in the controlled setting
846 (texture from PHOTEX database).

847 **Figure 4.** Manual (a) and semi-automatic (b) delineations of the proximal (1) and distal (2) lungs.
848 Ultrasound scan of fetal lungs, 4 cardiac chamber views at 37.0 weeks+days of gestational age.

849 **Figure 5.** Eroded ROIs from manual (a) and semiautomatic (b) delineations of the fetal lungs
850 (clinical data set). Original ROIs from a distal/proximal lung at 37.0 weeks+days of gestational
851 age.

852 **Figure 6.** Flowchart of the experiment design.

853 **Figure 7.** Flowchart of the robustness evaluation in relation to an acquisition parameter using a
854 texture (from OUTEX databased) acquired under different illumination conditions as example.
855 For each similarity measurement (Chebyshev and Correlation), a mean similarity value
856 [mean±std] in relation to illumination is obtained for texture T and each texture-based method
857 (z = 1...5). Then, for each similarity measurement the mean among all textures will be computed
858 obtaining a unique value for illumination and each method.

859 **Figure S.1.** Example of a fetal lung ultrasound texture and its histogram (a), and a selected (b)
860 and a non-selected (c) texture image and the corresponding histograms for the controlled Data
861 Set.

862 **Figure S.2.** Distribution of the resolution of the clinically acquired ultrasound images. Resolution
863 values are given as mm.

864 **Figure S.3.** Distribution of the rotation of the clinically acquired ultrasound images. Spine
865 orientation angle values are given as degrees.