

23 **Abstract**

24 The routine clinical breast ultrasound annotation method has the limitations of
25 time-consuming, inconsistent, inaccurate and incomplete notation. A novel 3-D
26 automatic annotation method for breast ultrasound imaging has been recently
27 developed, which used a spatial sensor to track and record conventional B-mode
28 scanning so as to provide more objective annotation. The aim of this study is to test
29 the feasibility of the automatic annotation method in clinical breast ultrasound
30 scanning. An ultrasound scanning procedure using the new method was established. A
31 comparison between the new method and the conventional manual annotation method
32 was performed with 46 breast cancer patients (49 ± 12 years). The time used for
33 scanning a patient was recorded and compared for the two methods. The
34 intra-observer and inter-observer experiments were performed and the intraclass
35 correlation coefficients (ICCs) were calculated to analyze the system reproducibility.
36 The results demonstrated that the average scanning time of using the new annotation
37 method was reduced by 36 s or 42.9% in comparison with the conventional method.
38 There were high correlations between the results of the two annotation methods ($r =$
39 0.933 , $P < 0.0001$ for distance, $r = 0.995$, $P < 0.0001$ for radial angle). Intra-observer
40 and inter-observer reproducibility were excellent, with all ICCs larger than 0.92. The
41 results showed that the 3-D automatic annotation method is reliable for clinical breast
42 ultrasound scanning and it can greatly reduce the scanning time. Although large-scale
43 clinical studies are still needed, this work verified that the new annotation method has
44 potential to be a valuable tool to help breast ultrasound examination.

45 **Key words:** Breast ultrasound, Breast imaging, Annotation, 3-D ultrasound,
46 Breast cancer, Clinical study

47

48 **Introduction**

49 Breast ultrasound is a common diagnosis method for patients with breast cancer
50 in clinics because it is non-invasive, real-time and less expensive (Dixon 2008; Huang
51 et al. 2008; Jackson 1990). It has good sensitivity in dense breasts and, thus, is
52 employed as a complementary method to mammography for breast screening (Chen et
53 al. 2004; Svensson 1997). In clinics, breast ultrasound can also be used to **differentiate**
54 benign from malignant lesions, which can help to reduce the number of biopsies (Cho
55 et al. 2006; Hong et al. 2005).

56 **Figure 1(a)** is a typical ultrasound display during breast examination, which
57 consists of an ultrasound image and a corresponding image annotation. The
58 annotation is used to register the image location with respect to the breast (American
59 College of Radiology 2011). Because the follow-up diagnosis, evaluation and
60 treatment are performed based on the stored annotation, it is crucial to provide
61 accurate and complete annotations. **The stored annotation is also very important for**
62 **surgery. The women with large tumors, such as a malignant lesion located across**
63 **different quadrants, are usually recommended to have the mastectomy (American**
64 **Cancer Society).** As shown in **Figure 1(a)**, there are two parts on the annotation,
65 graphic pictogram and textual sequence. **In the graphic pictogram, the circle**
66 **represents the breast region. The irregular part next to the circle means the arm, which**
67 **is used to indicate the laterality (left or right) of the breast. The arrow is the probe**
68 **icon, which represents the probe location. The arrow direction means the probe**
69 **direction and the movable arrow can be manipulated by the operator** to reflect the
70 current location of the ultrasound image. Most commonly, a trackball on the
71 ultrasound machine is employed to manipulate the position of the probe icon relative
72 to the breast marker region. There are three types of breast marker, as shown in
73 **Figure 1(b)**. The operator can choose a suitable pictogram to annotate the image
74 according to the image location. The spatial information is also indicated in the

75 textual sequence. In the **Figure 1(a)**, L means left breast, 3 represents 3 clock radial
76 direction and 4 indicates 4 cm to the nipple.

77 During breast examination, when one image is useful for diagnosis, a series of
78 complex hand motions need to be performed to annotate the image (Jackson and
79 Chenal 2006; Kuzara and Brown 2006). The **sonography operator** firstly freezes the
80 ultrasound image using the freeze button on the ultrasound machine. Then the
81 **sonography operator** changes the probe icon position according to the estimation.
82 Finally, **the textual sequence is typed** using the keyboard. In hospital, patient care and
83 productivity are the main concerns. However, this manual annotation method causes a
84 variety of issues.

85 One issue arises from the complex manual annotation procedure. The above
86 actions are repeated for every ultrasound image, which are time-consuming (Entrekin
87 2010). Compared with the breast scanning procedure, the annotation even takes more
88 time in the whole breast ultrasound examination, especially for new staff with little
89 experience. In China, the clinical practice guideline recommends that two operators
90 are needed in breast ultrasound examination (Chinese Medical Association 2004).
91 One manipulates the ultrasound machine to scan the breast and the other **records** the
92 image and **annotates** it. This method can effectively decrease the examination time.
93 But it is obviously a waste of human resources in healthcare institutions. In addition,
94 the highly repetitive annotation procedure is also fatigue causing for the operator.

95 **Another problem caused by the manual annotation method is subjective**
96 **registration of the image location, which** is set according to the estimation of the
97 probe location relative to the breast **by the sonography operator**. The manual
98 estimation depends on the **sonography operator's** training and experience, and may
99 lead to inaccurate results or even errors. Furthermore, different operators may
100 annotate images in their own way, which can cause inconsistency in image recording
101 (Brandli 2007). For example, as shown in Figure 1(a), some operators may type the
102 textual sequence near to the breast marker region while others may type it on the

103 ultrasound image. The inconsistent ultrasound images can cause difficulties to the
104 follow-up image processing or statistical analysis (Cupples et al. 2004). In addition, as
105 shown in **Figure 1(a)**, the 2-D annotation cannot display all spatial information in 3-D
106 space, such as the probe tilt angle. This can also cause problems to the downstream
107 evaluation and treatment. According to the incomplete spatial information, different
108 clinicians may have different judgements on the image location in 3-D space.

109 Compared with conventional B-mode ultrasound (2-D), 3-D ultrasound can
110 overcome limitations of 2-D viewing and measuring of 3-D anatomy (Chang et al.
111 2015; Fenster et al. 2011; Huang et al. 2005; Huang et al. 2015). The applications of
112 3-D breast ultrasound have been reported in the literature including the image
113 guidance of biopsy and surgery (Albrecht et al. 2006; Fenster et al. 2004; Tamaki et al.
114 2002; Weismann et al. 2000), breast cancer diagnosis (Kelly et al. 2010; Shipley et al.
115 2005; Kotsianos-Hermle et al. 2009; Kuo et al. 2008; Lin et al. 2012), image
116 evaluation of intraductal cancer spread (Sato et al. 1998), and mammary ducts
117 imaging in lactating women (Gooding et al. 2010). Compared with the above studies
118 at the stage of lab research, two 3-D breast ultrasound products have begun to be
119 applied in clinical diagnosis. One is Automated Breast Ultrasound (ABUS) of the GE
120 Healthcare and the other is the Automated Breast Volume Scanner (ABVS) of
121 Siemens. It was reported that the above automated 3-D breast ultrasound systems had
122 obvious advantages, including the higher diagnosis accuracy, less operator
123 dependency, and better lesion size prediction, compared with the conventional
124 hand-held 2D ultrasound (Chang et al. 2015a; Chang et al. 2015b; Lin et al. 2012).
125 However, for the above two systems, specially designed probes are required, which
126 are expensive and bulky for the clinical routine use. In addition, the sonography
127 operator cannot move the probe to the desired position freely because the moving
128 manner of the probe is predefined. Therefore, though 3-D breast ultrasound is a
129 promising imaging method, there is still a long way to go before it can be widely used
130 in routine clinical breast examination. 2-D ultrasound imaging is still the dominant
131 scanning mode for breast ultrasound examination, considering the equipment and

132 training costs of using 3-D system, the sophisticated experiences gained by clinicians
133 using 2-D ultrasound.

134 As the routine clinical examination tool, the existing breast ultrasound annotation
135 system has the problems of time-consuming, inconsistent, inaccurate and incomplete.
136 To overcome the problems of the existing manual annotation, a 3-D automatic
137 annotation system was developed (Jiang et al. 2014). A 2-D ultrasound scanner was
138 utilized in this system to capture the ultrasound images. An electromagnetic spatial
139 sensor was mounted to the ultrasound probe to obtain the positional information of the
140 images. The 3-D virtual models of breast and probe were employed to display the
141 image locations. The technical details including the system components, the
142 calibration method, the software development, the annotation parameters calculation,
143 the selection of reference points, and the annotation display method were reported in
144 the previous study (Jiang et al. 2014). The aim of this study is to evaluate the
145 feasibility of the newly developed 3-D automatic annotation system in clinical breast
146 ultrasound scanning on patients with breast tumors. The scanning procedure using the
147 automatic annotation method was established. The comparison between the new
148 method and the manual annotation method was performed. The reproducibility of the
149 method was also investigated.

150 **Methods**

151 *Patients*

152 This study was approved by the human subject ethics committee of the
153 institution and all patients gave the informed consent in this study. The experiments
154 were conducted in the Sun Yat-Sen University Cancer Center (Guangzhou, China). In
155 December 2013, 46 patients (all female patients; mean age, 49 years \pm 12 (standard
156 deviation); range, 24-65 years) who met the following criteria were prospectively
157 recruited. The inclusion criterion was presence of breast lesions in breast ultrasound
158 examination. 19 patients had benign lesions and 27 patients had malignant tumors (2

159 patients with ductal carcinoma in situ (DCIS), 20 patients with invasive ductal
160 carcinoma (IDC) and 5 patients with invasive lobular carcinoma (ILC)). Patients were
161 excluded if they had mastectomy before and one or two of their breasts were cut off.
162 This clinical study included two parts, which were the comparison study of manual
163 annotation method and the 3-D automatic annotation technique, and the
164 reproducibility test of this new annotation method. 21 of recruited patients
165 participated in the first part, and 25 of them participated in the second part of this
166 study.

167 *The 3-D automatic annotation method*

168 The novel annotation technique has been developed to provide 3-D, automatic
169 and continuous annotation for breast ultrasound imaging. Jiang et al. (2014)
170 previously reported the development of this method, and some key features were
171 described here. The new annotation system consisted of an ultrasound machine (DC-8,
172 Mindray, Shenzhen, China) with a linear 2-D probe (L12-3E, Mindray, Shenzhen,
173 China, 3.0-13.0 MHz), an electromagnetic spatial equipment (medSAFE, Ascension
174 Technology, Burlington, VT, USA) and a computer installed with a video capture
175 card (NI-IMAQ PCI/PXI-1411, National Instruments, Austin, TX, USA) and a
176 customized program, as shown in **Figure 2**. The spatial equipment was comprised of
177 a spatial sensor, a control box and a transmitter. The spatial sensor was fixed on the
178 ultrasound probe using a custom-designed mounting kit, also shown in **Figure 2**.
179 Real-time spatial information (three positions (x, y, z) and three orientations (azimuth,
180 elevation, roll)) of probe were captured by this sensor and sent to the computer
181 through the control box. During scanning, ultrasound images from the ultrasound
182 scanner were also sent to the computer through a video capture card.

183 The ultrasound images and the corresponding spatial data were acquired by a
184 custom-developed program, with its interface shown in **Figure 3**, which contained the
185 tool bar and display window. The display window was divided into two parts,
186 annotation window (left part of the display window) and image window (right part of

187 the display window). During the breast scanning, ultrasound images were displayed
188 on the image window. Meanwhile, the corresponding annotations were shown on the
189 annotation window in real time. In this annotation method, four types of display
190 modes were used, including the 2-D annotation pictogram, textual annotation
191 sequence, 3-D annotation models and annotation value, as shown in **Figure 3**. The
192 first two annotation modes were used in conventional annotation method, which were
193 familiar to clinicians. The 3-D models including breast model and probe model were
194 adopted in this system to intuitively annotate the image location. By changing the
195 position of probe model on the breast model, the image location could be displayed.
196 The 3-D annotation models can display all spatial information such as the probe tilt
197 angle which cannot be indicated in conventional annotation method. The accurate
198 values of image distance to nipple and radial angle were displayed by the mode of
199 annotation value. All these spatial indicators including the arrow of 2-D pictogram,
200 textual sequence, 3-D probe model and the annotation values were changed
201 automatically according to the spatial data from spatial sensor when ultrasound probe
202 moved across the breast.

203 In this system, the positional data were acquired by the spatial sensor. A
204 cross-wire phantom was used to establish the offsets between the spatial sensor and
205 the ultrasound probe (Barry et al. 1997). Based on the spatial data of the sensor and
206 the calibration matrix, the positional information in 3-D space of the ultrasound image
207 could be calculated. Then the positional information was displayed using the above
208 four types of display modes. However, in this annotation method, the sizes of 3-D
209 breast model and the 2-D pictogram were established in advance. For different
210 patients, the sizes of breasts are different. To resize the actual breast to the breast
211 model, four reference points, including the nipple points of left and right breasts, and
212 border points of left and right breasts, were used in this method. Before each scanning,
213 the operator held the probe and puts it on the nipple point and border point of each
214 breast. The spatial data of the four points were recorded by the system. Then the
215 radius and height of the actual breasts were calculated and scale parameters between

216 the actual breast and breast model were obtained. According to the scale parameters
217 and the calibration matrix, the spatial data acquired using the spatial sensor was then
218 automatically displayed on the annotation model.

219 *Development of a clinical procedure using the 3-D automatic annotation method*

220 In clinical breast ultrasound scanning, a foot switch was connected to the
221 computer of this system to achieve functions of computer mouse so it can control the
222 action of the software such as the acquisition of ultrasound image. This design could
223 help the operator to release hand from the computer mouse during scanning the breast.
224 During the scanning, the patient lay on the bed in supine position with her arms
225 abducted and hands under the head to flatten the breast. To reduce the influence of
226 patient motions, the patient was asked to keep still during the scanning procedure and
227 lighten her breath as possibly as she could. At the beginning of the scanning, the
228 software prompted the physician to record the four reference points. The physician
229 put the probe on the corresponding point of the breast, stepped on the foot switch, and
230 the spatial data of this point was recorded by the software. The software then
231 reminded the operator to record the next reference point until four reference points
232 were captured. After that, the ultrasound image from the probe and the corresponding
233 annotation were displayed on the interface of the software (**Figure 3**) and the
234 physician could begin the breast scanning. In this study, the physician held the
235 ultrasound probe to scan across the breast in orthogonal antiradial scanning pattern
236 (Stavros 2004), which is one of the most common scanning patterns in clinics. During
237 scanning, ultrasound images and their annotations changed in real time. If an
238 ultrasound image contained the information of lesion, the physician stepped on the
239 foot switch and this image together with its annotation was saved. This action took
240 less than one second and there was almost no influence to the whole scanning
241 procedure. The scanning continued until both of the two breasts were covered and all
242 images of lesions were saved. The scanning procedure is shown in **Figure 4**. **During**
243 **scanning, if the patient has any motion which breaks the continuous scanning, it is**
244 **necessary to define the reference points again before continuing the scanning.**

245 *Comparison study between manual annotation and 3-D automatic annotation*

246 To investigate the performance of the new annotation method, the comparison
247 between the 3-D annotation method and the clinical manual annotation was performed.
248 21 patients (all female patients; mean age, 49 years \pm 12 (standard deviation); range,
249 25-65 years) were contained in this comparison test. A physician who has 3 years'
250 experience in breast ultrasound was involved in this study. The annotation time and
251 results using the two methods were compared. The ultrasound machine and probe
252 were the same in the two annotation methods.

253 *Ultrasound examination*

254 In this comparative experiment, results of two annotation methods on the same
255 lesion were compared. To ensure that the ultrasound probe was put on the same
256 position in two scanning procedures, the patient was asked to keep stationary until
257 two annotations were completed. In addition, before the comparative scanning, an
258 extra ultrasound scanning was performed so that the physician could investigate the
259 lesion and found a suitable position of the probe on the breast to record the ultrasound
260 image. In the following comparative scanning, the operator would put the probe on
261 the same location and annotate the ultrasound image.

262 The patient lay on the bed and the physician held the probe to scan two breasts in
263 orthogonal antiradial scanning pattern. After two breasts were covered, the physician
264 swept the probe to the lesion region to investigate the ultrasound images of this lesion.
265 The operator adjusted the probe to get the suitable image which could clearly display
266 the lesion. The probe location and ultrasound image were remembered in the mind by
267 the operator as the reference of the following scanning.

268 *3-D automatic annotation*

269 After the ultrasound examination, a scanning procedure using the developed 3-D
270 automatic annotation method was performed by the physician. The scanning and

271 annotation procedure was described in the previous section. In this procedure, the
272 program interface (**Figure 3**) was displayed on the computer. When the suitable
273 ultrasound image was found, the operator acquired this image together with its
274 annotation by stepping on the foot switch. This action was repeated if another lesion
275 was found until two breasts were scanned. The time of the whole scanning procedure
276 including the definition of four reference points was recorded. The recorded scanning
277 time did not include that spent on the preparation work of the computer setup, spatial
278 equipment initiation, and the ultrasound machine setup. The whole preparation work
279 took about 2 min. The setup would only be performed once and could be used for all
280 patients until the system was shut down.

281 *Manual annotation*

282 Following the 3-D automatic annotation procedure, manual annotation was
283 performed by the same physician. In this procedure, the physician used the ultrasound
284 machine interface. The orthogonal antiradial scanning pattern was also adopted in
285 manual annotation scanning. After two breasts were covered, the physician moved the
286 probe to the lesion region to find the suitable ultrasound image. When such an image
287 was found, the operator froze the ultrasound image to annotate it. The physician
288 firstly chose a suitable graphic pictogram from the three types of graphic pictograms
289 (**Figure 1(b)**). According to the laterality of the lesion, one graphic pictogram was
290 chosen using the tracking ball of ultrasound machine. The physician then changed the
291 arrow position and orientation on the graphic pictogram according to her estimation
292 on actual probe location. Finally, the physician typed the textual sequence using the
293 keyboard of the ultrasound machine. When the above three steps were finished, this
294 ultrasound image was completely annotated and saved. If there were more than one
295 lesion, this annotation procedure was repeated for each lesion.

296 *Reproducibility test of the 3-D automatic annotation method*

297 To further study the performance of this new annotation method, the
298 reproducibility test in clinical settings was performed. In total, 25 patients (all female
299 patients; mean age, 49 years \pm 12 (standard deviation); range, 24-65 years) involved in
300 this test. Besides the first physician involved in the above comparison test, the second
301 physician who also has 3 years' experience in breast ultrasound attended this test.
302 Before the reproducibility assessment, an extra ultrasound examination similar to the
303 above comparison test was conducted. In this examination, both of the two physicians
304 scanned the breasts and found the same suitable position for each breast lesion as the
305 reference of the later reproducibility test.

306 The reproducibility test included intra-observer and inter-observer repeatability
307 assessment. The patient was scanned and annotated by the first physician using the
308 3-D automatic annotation method twice with a 15 minutes interval for the
309 intra-observer repeatability. During the scanning, the patient lightened her breath as
310 possibly as she could. During the interval, the patient could breathe normally but keep
311 still. For the inter-observer repeatability assessment, the second physician repeated the
312 scanning using the same annotation system. The other data for inter-observer
313 repeatability analysis was from the first data set of the intra-observer repeatability
314 assessment.

315 *Data analysis*

316 In the manual annotation method, only parameters of the radial angle and the
317 distance to nipple were annotated with numerical value. Values of the two parameters
318 were compared in the two annotation methods. The Pearson correlation coefficient r
319 was calculated to assess the correlation between the manual and 3-D automatic
320 annotation methods. The scanning times on different patients using the two methods
321 were compared. To assess the system reproducibility, the intraclass correlation
322 coefficient (ICC) for intra-observer test and inter-observer test was used. A P value of
323 less than 0.05 was considered to indicate a significant difference. All statistical

324 evaluations were performed using the statistical software (SPSS for Windows, version
325 17.0; SPSS, Chicago, IL, USA).

326 **Results**

327 *Scanning time*

328 Among 21 patients that were scanned in the comparative study, 18 of them had
329 one lesion, two patients had two lesions and one patient had three lesions. The
330 scanning times were summarized in **Table 1**. *Student's t-test was used to analyze the*
331 *scanning time and a significant difference ($P < 0.001$) was demonstrated* between the
332 two annotation methods (84s for manual method, 48s for automatic method). For
333 patients with one lesion, the average difference was 36 s, which took 42.9% of the
334 whole manual scanning time (84 s). For the two methods, the scanning procedures
335 were almost the same so the time difference was mainly caused by the annotation
336 procedure. This automatic annotation could obviously save scanning time. Moreover,
337 as shown in **Table 1**, when there was more than one lesion, the time difference
338 became larger. That was because the manual annotation procedure was repeated for
339 each lesion which spent much time in the whole scanning procedure. While in the
340 new automatic method, the annotation procedure took little time in the whole
341 scanning examination. Therefore, the increased breast lesion had little influence on
342 the whole scanning time.

343 *Annotation results comparison between the manual and automatic methods*

344 **Figure 5** shows the typical annotation results of the manual method and the
345 automatic method for the same breast lesion. In the manual annotation, the
346 quantitative values were given by the textual sequence. The distance to the nipple was
347 indicated by the last number in the sequence in centimeters, as shown in **Figure 5(a)**.
348 The radial angles were expressed in clock format and they were changed to values in
349 degree. For the automatic method, the quantitative values of the two parameters were
350 displayed on the interface, as shown in **Figure 5(a)**. **Table 2** is the Person correlation

351 coefficient of the two annotation methods ($r = 0.933$, $P < 0.0001$ for distance, $r =$
352 0.995 , $P < 0.0001$ for radial angle), which demonstrated excellent positive
353 correlations with respect to the two analyzed parameters. The correlation plots and the
354 Bland-Altman plots are shown in **Figure 6**.

355 *Repeatability of automatic annotation method*

356 As shown in **Table 3**, for the measurement of distance, the intra-observer ICC
357 was 0.989 (95% confidence interval: 0.976, 0.995) and inter-observer ICC was 0.927
358 (95% confidence interval: 0.840, 0.968). For the parameter of radial angle, values of
359 ICC were both 0.998 (95% confidence interval: 0.995, 0.999). Excellent repeatability
360 was indicated by these results.

361 **Discussion**

362 In this clinical experimental study, we were able to demonstrate that the new
363 annotation method can provide 3-D automatic annotation for breast ultrasound
364 examination. The 3-D automatic annotation method helped save scanning time
365 compared with the existed manual annotation method, especially for patients with
366 more than one lesion. The annotation results showed excellent correlation with the
367 current clinical annotation method. In addition to the spatial data used in conventional
368 method, this developed method could provide probe tilt angle, which helped record
369 the complete spatial information of the ultrasound image in 3-D space. **All the spatial**
370 **data could be stored and displayed using the developed software in the follow-up**
371 **examination.** Quantitative measurements in intra-observer and inter-observer
372 assessment were reproducible.

373 In the light of potential future clinical application of the 3-D automatic
374 annotation method, there were several limitations in this study. **One limitation is that**
375 **the detection range of the electromagnetic spatial sensor is 46cm (medSAFE Manual,**
376 **Ascension Technology).** In this study, to ensure that the patient was in the detection
377 **range, the transmitter was fixed on the scanning bed and the patient was asked to lie**

378 as near as possible to the transmitter. However, it is inconvenient for the scanning
379 because the breast is close to the transmitter. In addition, the obese patients may be
380 out of the detection range. To solve this problem, in the future study, a planar
381 transmitter with larger detection range such as the Aurora sensor of Northern Digital
382 (Hummel et al. 2008) can be used. In this study, before scanning, the patients had to
383 remove all metallic wears and electronics goods to avoid the influence to the magnetic
384 field. Another limitation is that the experimental results were obtained based on the
385 condition that patients kept stationary and lightened their breath as possibly as she
386 could. The involuntary movements or breath may cause errors to our annotation
387 because these motions change positions of reference points while the new spatial data
388 cannot be updated. Motion compensation has been studied in different fields such as
389 surface modeling in reconstructive surgery and ultrasound imaging for residual limb
390 assessment (Patete et al. 2009). One useful method is to place markers on the surface
391 and use cameras to track these marks to further measure the movements (Patete et al.
392 2009; Sanders and Lee 2008). Another solution reported is the motion compensation
393 methods based on image features (Douglas et al. 2002; Xue et al. 1997; Zheng et al.
394 2001). In this automatic annotation system, instead of increasing cameras, another
395 spatial sensor can be used to track the motion. This sensor can be attached on the body
396 of patient and the data from this sensor are acquired in real time. The initial positional
397 data is recorded. When there is movement, the difference can be obtained so the
398 spatial data of reference points can be modified according to this difference. Another
399 limitation of this new annotation method is the deformation of the soft breast tissue.
400 During clinical breast ultrasound scanning, a certain force is applied on the breast
401 when the probe sweeps across the breast. This force can cause the breast deformation,
402 which may affect results of the annotation. Different methods have been proposed to
403 solve the problem of soft tissue deformation (Crum et al. 2004; Gee et al. 2003; Guo
404 et al. 2006; Khallaghi et al. 2012; Krucker et al. 2002; Leung et al. 2009; Lu et al.
405 2009a; Lu et al. 2009b; Treece et al. 2002; Xiao et al. 2002). One approach is the use
406 of non-rigid registration methods (Crum et al. 2004; Guo et al. 2006; Leung et al.
407 2009). It was demonstrated that the registration method could help to correct the

408 deformations over 85% in validation experiments (Krucker et al. 2002). Another
409 study reported that the registration error was less than 0.19 mm when this method was
410 used to register breast deformations on ultrasound images (Xiao et al. 2002). A
411 feature-based registration algorithm was reported and the experiments demonstrated
412 its potential for recovering non-rigid deformations (Khallaghi et al. 2012). The
413 combination of non-rigid registration method and the optical sensing device has also
414 been proposed to assess the deformations in 3-D ultrasound scanning (Gee et al. 2003;
415 Treece et al. 2002). On the basis of these studies, non-rigid registration method will
416 be developed for our annotation system to correct the breast deformation during the
417 clinical scanning. Compared with conventional manual annotation method,
418 time-saving is an obvious advantage of this developed annotation method, especially
419 for patients with more than one lesion. However, in this study, only three patients
420 with multiple lesions were analyzed. Additional studies are needed to specially study
421 cases with multiple lesions to further demonstrate the value of the 3-D automatic
422 annotation method. **Considering the clinical applications, the use of a spatial sensor
423 makes the scanning system more complicated. In addition, as previously described,
424 the preparation work, including the computer setup and the spatial equipment
425 initiation, also increases the setup time. In future study, the spatial sensor can be
426 integrated to the ultrasound probe and the software can be combined into the interface
427 of the ultrasound machine to facilitate the clinical use.**

428 Despite these restrictions of this study, our results suggest that the developed
429 annotation method has the potential to overcome limitations of the current manual
430 annotation method. The use of quantitative spatial data from the spatial sensor instead
431 of operator subjective estimation to annotate the ultrasound image is an important step
432 toward more accurate diagnosis results. Another improvement is that automatic
433 annotation procedure, which can help physician avoid high repetitive work and save
434 examination time. This advancement has opened up the opportunity to provide breast
435 ultrasound to more patients with current clinical conditions. The implementation of
436 this developed annotation method is another milestone. Unlike the current 3-D

437 ultrasound scanners (Kelly et al. 2010; Lin et al. 2012; Nelson and Pretorius 1998;
438 Porter and Seck 2009; Rao and Varghese 2008; Shung 2002; Tozaki et al. 2010), which
439 need a specially designed ultrasound machine, this method is based on the routine 2-D
440 scanner and only a spatial sensor is attached on the probe. In addition, with the
441 development of ultrasound technique, the electromagnetic spatial sensor has been
442 integrated to the ultrasound scanner system (Thiele and Chang 2003). Based on such
443 equipment, the 3-D automatic annotation method is easily to be implemented.

444 In conclusion, the present study indicated that the 3-D automatic annotation
445 method was feasible in clinical breast ultrasound examination and had advantages
446 compared with current manual annotation method. With the further improvement of
447 this method and large-scale clinical tests, this new annotation method is expected to
448 facilitate clinical breast ultrasound examination.

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452

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577

578 **Tables**

579 Table 1. Scanning time comparison results of manual annotation method and the 3-D
 580 automatic annotation method

	Time for 1 lesion (s)		Time for 2 lesions (s)		Time for 3 lesions (s)
	Average	Range	Average	Range	One patient
Manual annotation	84.0	61.0-121.0	132.0	131.0-133.0	189.0
Automatic annotation	48.0	27.0-79.0	65.5	62.0-69.0	76.0
Difference	36.0	28.0-47.0	66.5	64.0-69.0	113.0

581

582 Table 2. Correlation results of distance to nipple and radial angle with 3-D automatic
583 annotation method in comparison with manual annotation method

Parameter	P Value	Pearson r
Distance to nipple	<0.0001	0.933
Radial angle	<0.0001	0.995

584

585

586 Table 3. Repeatability results of the developed 3-D automatic annotation method in
587 intra-observer and inter-observer assessment

	Intra-observer ICC	Inter-observer ICC
Distance to nipple	0.989	0.927
Radial angle	0.998	0.998

588

589

590 **Figure Captions**

591 Figure 1. A typical ultrasound display in breast examination. (a): the typical
592 annotation components including the graphical pictogram and the textual sequence.

593 (b): three common types of graphic pictogram.

594 Figure 2. The components and modules used for the 3-D automatic annotation system.

595 Figure 3. The software interface of the 3-D automatic annotation system.

596 Figure 4. The flow chart of the scanning procedure using the new 3-D automatic
597 annotation method.

598 Figure 5. A typical annotation results of the manual and automatic methods for the
599 same breast lesion. (a): the manual annotation result. (b): the automatic annotation
600 result.

601 Figure 6. The scatter plots (left) and Bland-Altman plots (right) of the analyzed
602 parameters for the two annotation methods. Excellent correlations were found
603 between the two annotation methods. SD = standard deviation.

604

Figure 1
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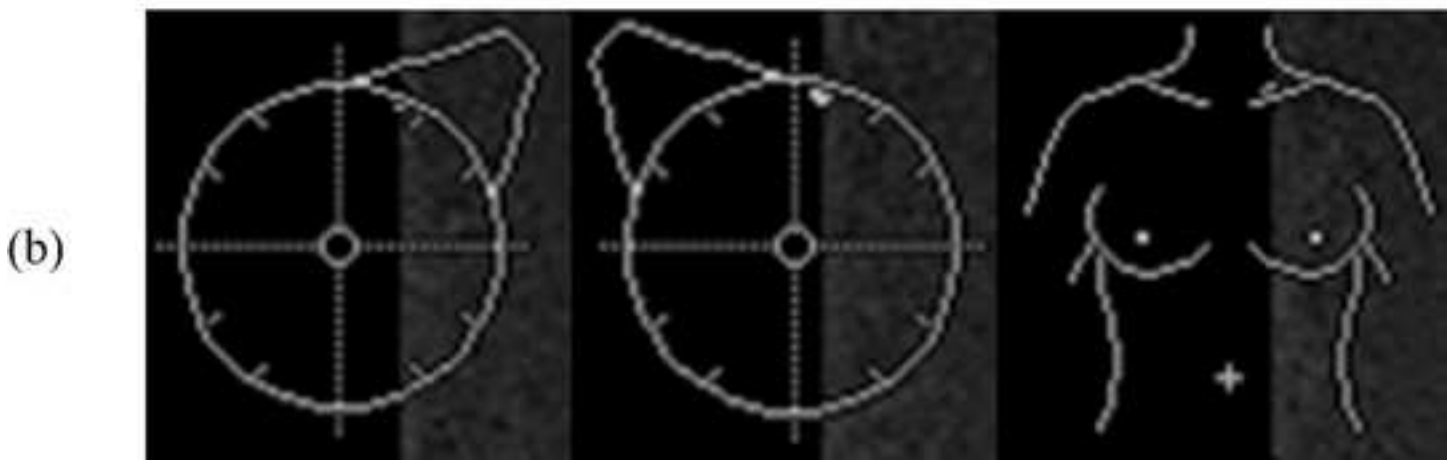
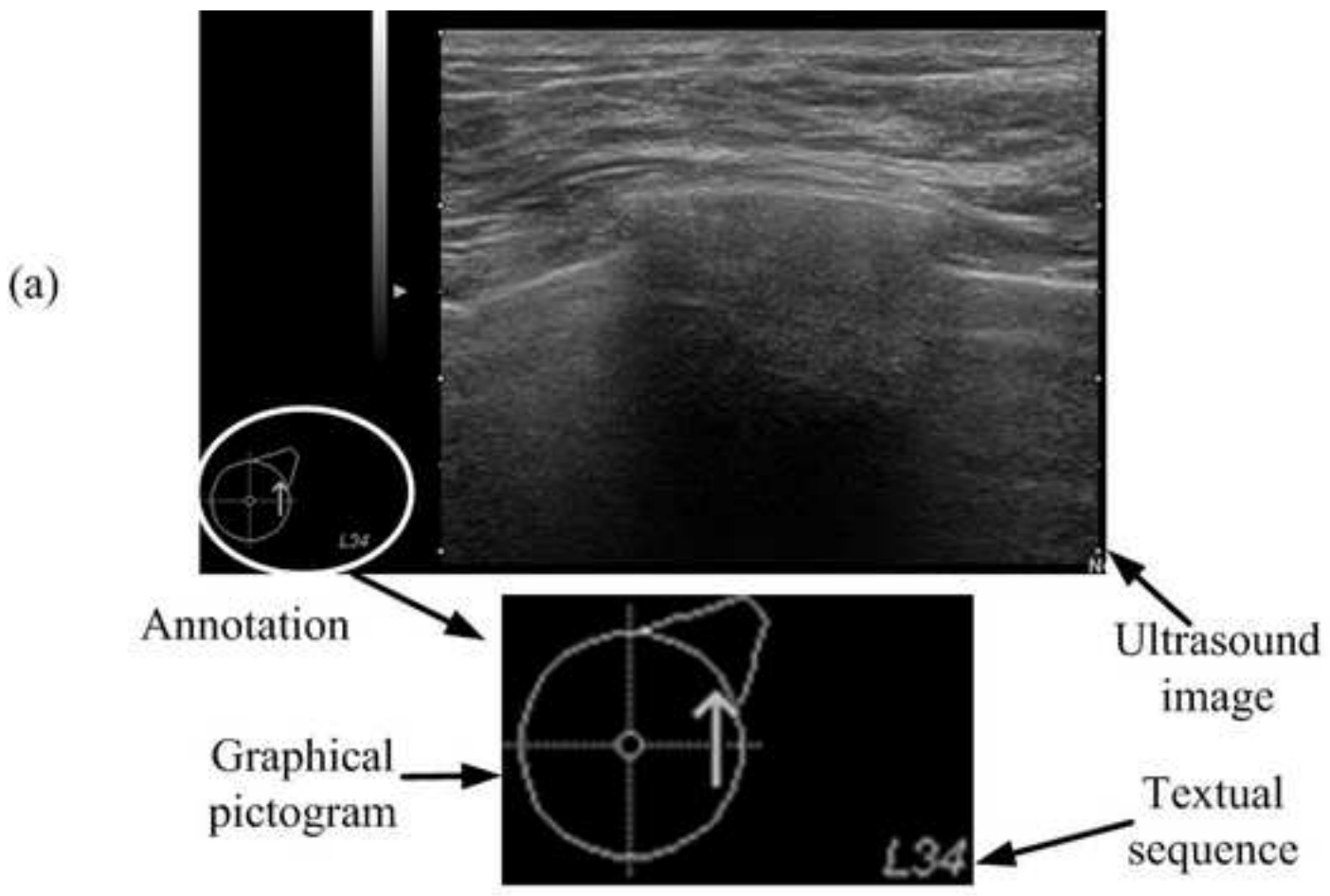


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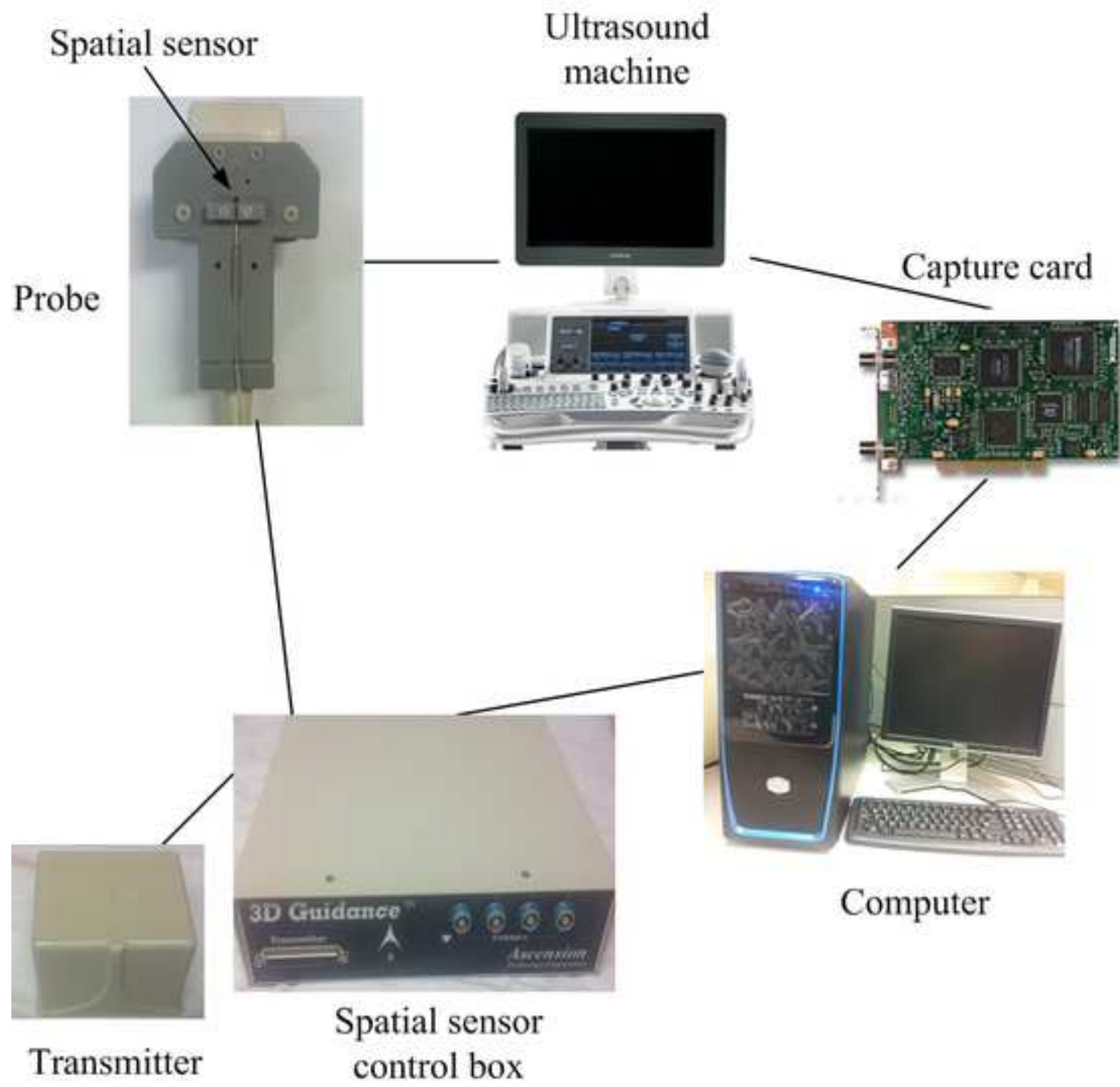


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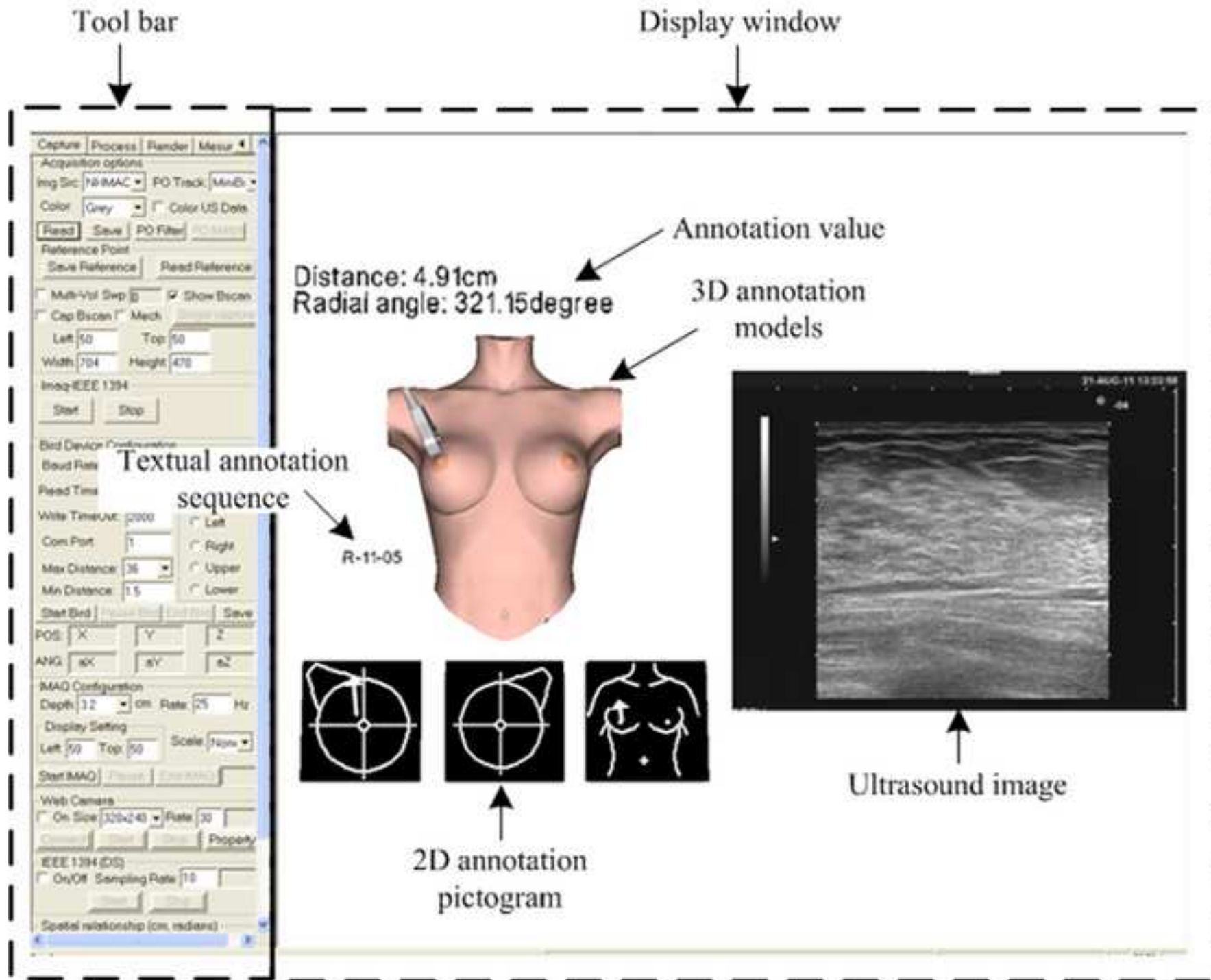
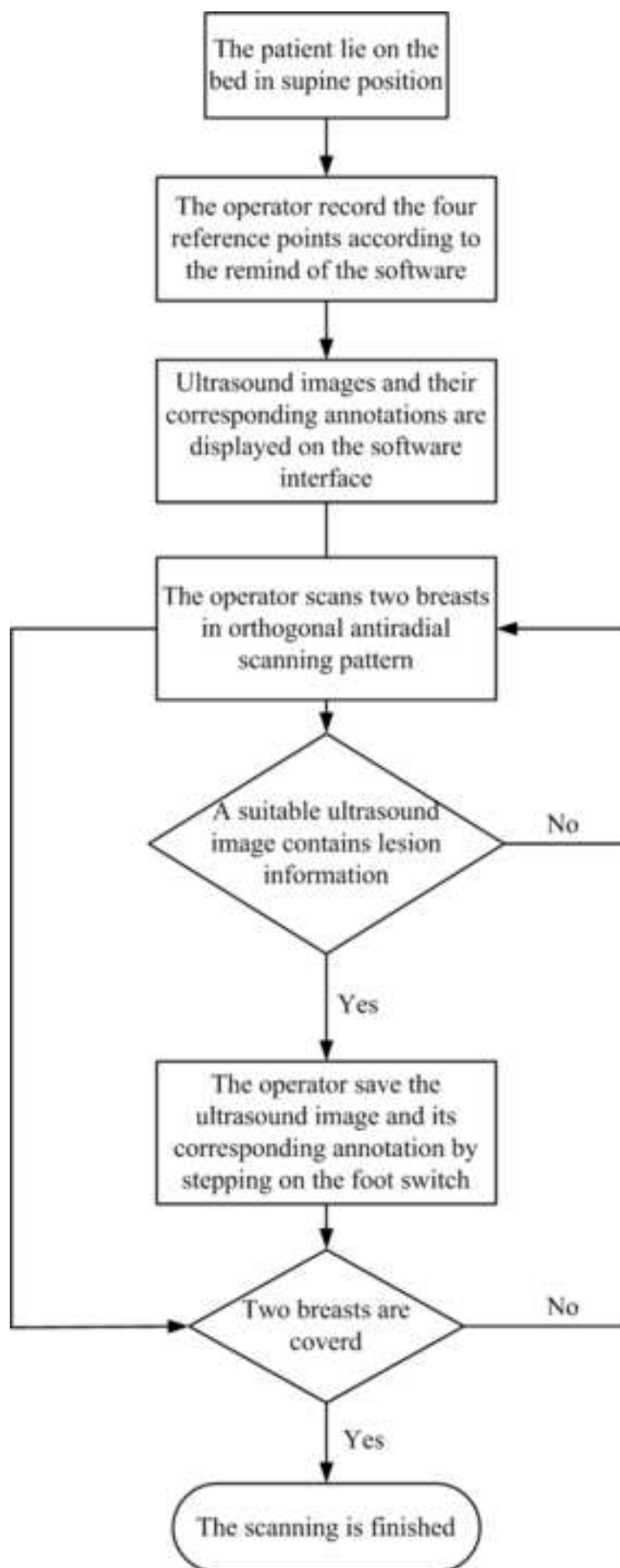
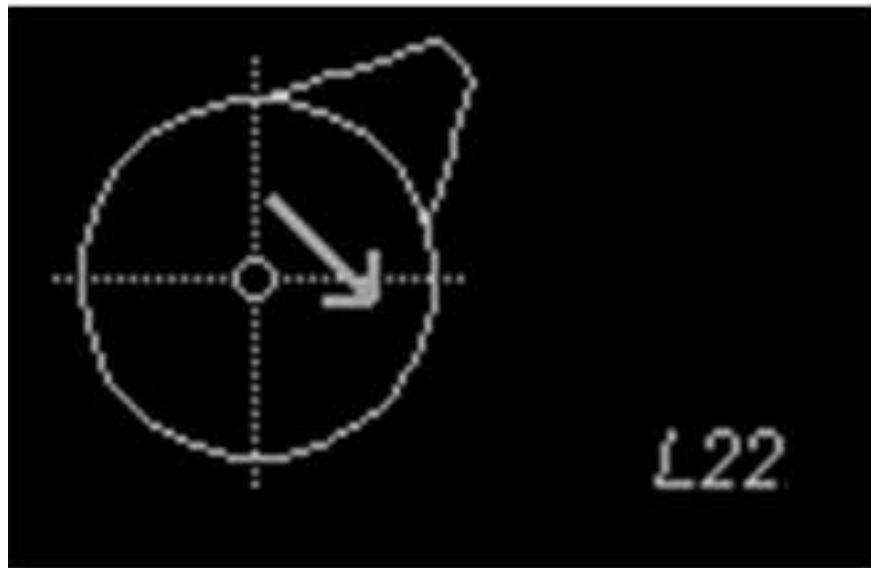


Figure 4

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(a)



(b)

Distance: 2.37cm
Radial angle: 67.53degree

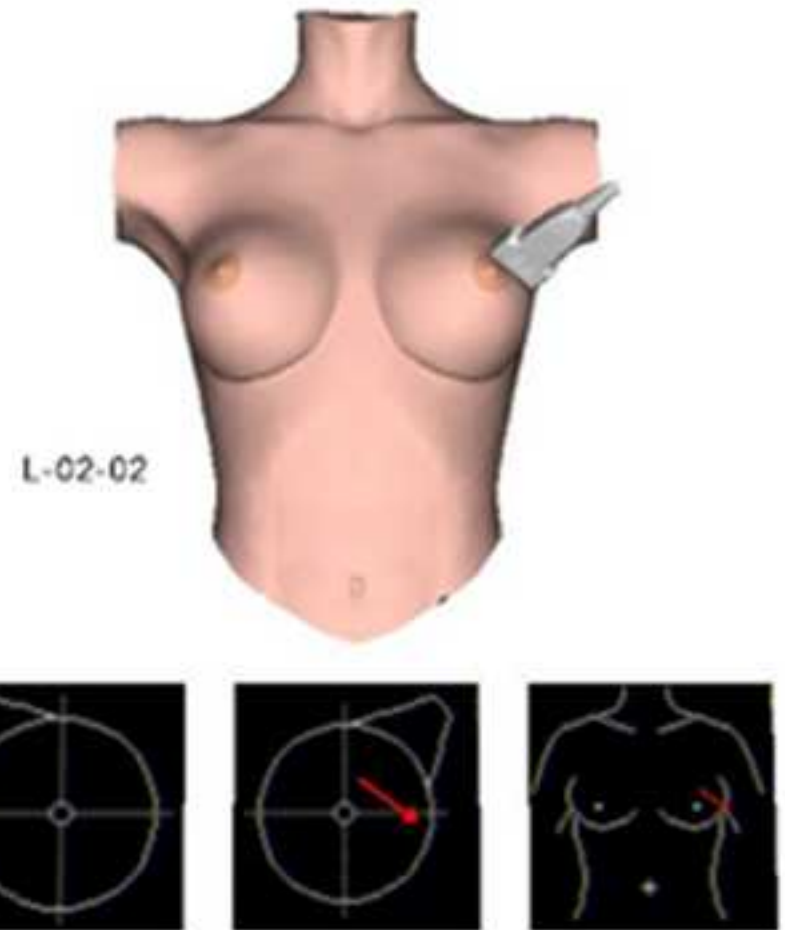


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