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AN ANALYSIS OF THE SEGMENTATION THRESHOLD USED IN AXIAL-SHEAR STRAIN ELASTOGRAPHY

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Abstract

Axial - shear strain elastography was introduced recently to image the tumor-host tissue boundary bonding characteristics. The image depicting the axial-shear strain distribution in a tissue under axial compression was termed as an axial-shear strain elastogram (ASSE). It has been demonstrated through simulation, tissue-mimicking phantom experiments, and retrospective analysis of *in vivo* breast lesion data that metrics quantifying the pattern of axial-shear strain distribution on ASSE can be used as features for identifying the lesion boundary condition as loosely-bonded or firmly-bonded. Consequently, features from ASSE have been shown to have potential in non-invasive breast lesion classification into benign versus malignant. Although there appears to be a broad concurrence in the results reported by different groups, important details pertaining to the appropriate segmentation threshold needed for – 1) displaying the ASSE as a color-overlay on top of corresponding Axial Strain Elastogram (ASE) and/or sonogram for feature visualization and 2) ASSE feature extraction are not yet fully addressed. In this study, we utilize ASSE from tissue mimicking phantom (with loosely-bonded & firmly-bonded inclusions) experiments and freehand –acquired *in vivo* breast lesion data (7 benign & 9 malignant) to analyze the effect of segmentation threshold on ASSE feature value, specifically, the “*fill-in*” feature that was introduced recently. We varied the segmentation threshold from 20% to 70% (of the maximum ASSE value) for each frame of the acquisition cine-loop of every data and computed the number of ASSE pixels within the lesion that was greater than or equal to this threshold value. If at least 40% of the pixels within the lesion area crossed this segmentation threshold, the ASSE frame was considered to demonstrate a “*fill-in*” that would indicate a loosely-bonded lesion boundary condition (suggestive of a benign lesion). Otherwise, the ASSE frame was considered not to demonstrate a “*fill-in*” indicating a firmly-bonded lesion boundary condition (suggestive of a malignant lesion). The results demonstrate that in the case of *in vivo* breast lesion data the appropriate range for the segmentation threshold value seems to be 40% to 60%. It was noted that for a segmentation threshold within this range (for example, at 50%) all of the analyzed breast

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lesion cases can be correctly classified into benign and malignant, based on the percentage number of frames within the acquisition cine-loop that demonstrate a “fill-in”.

Keywords

Axial-shear strain; Benign; Breast; Elastography; Malignant; Segmentation Threshold

1. INTRODUCTION

Quasi-static elastography was introduced in the early 1990s (Ophir et al. 1991) to provide a way to visualize the mechanical properties of target tissue. This has now become a regular imaging option available in several clinical ultrasound scanners. Most of these scanners with an elastography option provide an image of the local axial strains experienced by the tissue due to a small external compression (cf. Garra 2011, Balleyguiera et al. 2013, Bamber et al. 2013). These images of the axial strain distribution are usually referred to as Axial Strain Elastograms (ASE), or elastograms for simplicity (Bamber et al. 2013, Ophir et al. 2011, Parker et al. 2011). The ASE provides information relating to the elastic property of the target tissue. Specifically, contrast between different tissues is produced when tissue regions with different stiffness parameters experience different levels of axial strain than those in surrounding tissues; a stiffer tissue region will generally experience less strain than a softer one (Céspedes et al. 1993; Ophir et al. 1999).

However, soft tissue under a small quasi-static compression not only experiences axial strain, but also other strains like lateral strain, axial-shear strain, lateral-shear strain. Recently, axial - shear strain elastography was introduced to image the tumor-host tissue boundary bonding characteristics (Thitaikumar et al. 2005, 2007). The image depicting the axial-shear strain distribution in a tissue under axial compression was termed as an axial-shear strain elastogram (ASSE). It is important to note that the contrast mechanism in ASSE is due to the shear stress transfer that occurs at boundaries having elastic contrast (Thitaikumar et al. 2007). Thus, ASSE helps in visualizing information relating to the bonding conditions at the inclusion boundary and thereby provides additional information to that obtained from ASE. Imaging this additional information might be important in some clinical applications. For e.g., it is known that among breast lesions, malignant tumors are generally more firmly bonded to their surroundings than are benign tumors (Fry 1954).

It has been demonstrated through simulation, tissue-mimicking phantom experiments, and retrospective analysis of *in vivo* breast lesion data that metrics quantifying the pattern of axial-shear strain distribution can be used as features for identifying the lesion boundary condition as loosely-bonded or firmly-bonded. Consequently, features from ASSE have been shown to have potential in non-invasive breast lesion classification into benign versus malignant. Specifically, the following two features were reported as promising –

1. The normalized axial-shear strain area (NASSA) present at and outside the inclusion boundary (Thitaikumar et al. 2007, 2008, Xu et al. 2010, Varghese 2011);

2. Presence or absence of non-zero axial-shear strain values inside the inclusion (referred to as a “*fill-in*”) along with contrasting margin at the boundary (Thittai et al. 2010, Galaz et al. 2009, Thittai et al. 2012).

The NASSA feature was demonstrated to be useful in the case of geometrically symmetric inclusions (with respect to axis of compression). It was shown that NASSA feature from ASSE can improve the specificity, without compromising sensitivity, of non-invasive breast lesion classification (Thittai et al. 2008, 2011, and 2013). These findings were independently corroborated at least by one other group (Xu et al. 2010, Varghese 2011). The typical appearance of the axial-shear strain pattern due to a stiff inclusion has however been corroborated by several other groups as well (Chen et al. 2010, Garcia et al. 2009, Sayed et al. 2013, Maurice et al. 2013).

The “*fill-in*” as a feature was demonstrated to be useful to infer about the boundary bonding conditions of geometrically asymmetric inclusions (with respect to axis of compression). However, these demonstrations were done merely through few examples from *in vivo* breast lesion data archives (Thittai et al. 2010). We are currently collecting prospective *in vivo* breast lesion data to further study the clinical usefulness of this feature. Nevertheless, observation of this feature in ASSE has been independently corroborated by other groups as well (Chen et al. 2010, Xu et al. 2012, Maurice et al. 2013).

Although there appears to be a broad concurrence in the results reported by different groups, important details pertaining to the appropriate segmentation threshold needed for – 1) displaying the ASSE as a color-overlay on top of corresponding ASE and/or sonogram for feature visualization and 2) ASSE feature extraction are not yet fully addressed. A brief background on the various thresholds reported in the literature is given below.

In the early work reported in Thitaikumar et al. (2007) the effect of segmentation threshold on the NASSA feature value was studied using simulated elastic phantoms with a set inclusion-background modulus contrast, and a fixed applied axial compression. Based on this analysis a segmentation threshold value of 25% of the applied axial strain was used for the remainder of the parametric analysis reported in that paper. However, although the *in vivo* breast lesion data reported in Thitaikumar et al. (2008) was acquired by applying a fixed axial-compression, the lesion-background stiffness contrast was an unknown across the different cases. Therefore, a semi-automatic method was adopted that allowed the observer to outline a region of interest (ROI) in ASSE and an arbitrary segmentation threshold of 70% of the mean of the axial-shear strain value within the ROI was used to automatically compute the NASSA feature value. Xu et al. (2010) reported using a segmentation threshold of 20% of the applied axial strain in simulations, but adjusted this empirical value based on an estimate of the lesion-background strain contrast from ASE to account for the differences in stiffness contrast among the *in vivo* breast lesion cases. Recently (Thittai et al. 2011), an observer study on a database containing larger number of *in vivo* cases was reported that used a segmentation threshold value of 50% of the peak axial-shear strain value. The study also reported the finding that displaying ASSE as a color-overlay was preferred by the observers consisting of radiologist and sonographers. Clearly, several different segmentation thresholds have been used for analyzing the ASSE of *in vivo*

breast lesion data. Therefore, there is a need to understand and arrive at a desirable segmentation threshold, or a range, for extracting ASSE features and also for use in displaying ASSE as a color –overlay in real-time during freehand acquisition.

2. MATERIALS AND METHODS

In this study, we utilize ASSE from tissue mimicking phantom experiments and freehand –acquired *in vivo* breast lesion data to analyze the effect of segmentation threshold on ASSE feature value. As mentioned in the previous section, there are at least two feature values of interest from ASSE. The effect of segmentation threshold on NASSA value has been studied in simulations, and several different empirical threshold values have been used for *in vivo* data analysis. However, the effect of segmentation threshold on the computation of the “fill-in” feature from ASSE has not been investigated at all. Therefore, our objective in this work is to study the segmentation threshold effect on the “fill-in” feature through analysis of the ASSE. The applicability of the results from this study to the NASSA feature reported in the literature will be discussed as well.

2.1 Tissue-mimicking Phantom data

Tissue-mimicking phantoms from gelatin-agar-water mixtures were manufactured and used for the experiments. The formula for manufacturing these phantoms has been described by many research groups (c.f., Hall et al. 1997, Kallel et al. 2001). For this study, phantom geometry consisted of a homogeneous cuboid with a cylindrical (elliptical cross-section) inclusion of contrasting Young’s modulus running horizontally through the center of the cuboid. The elliptical inclusion was oriented non-normally to the compression surface to make it geometrically asymmetric with respect to the axis of compression. Note that we were interested in making phantom with an inclusion that is stiffer than the background. We did not make independent Young’s modulus measurement on these phantoms. However, based on the relative gelatin concentrations in the background and the inclusion we expected the inclusion-background modulus ratio to be approximately 3 (Kallel et al. 2001). The inclusion was made to be either firmly-bonded or loosely-bonded to the background. Detailed description for manufacturing these elliptical inclusion phantoms can be found in Thittai et al. (2010). The phantom was submerged in water during imaging. The experiments were done using a Sonix-500RP scanner (Ultrasonix Medical, Richmond, BC, Canada) with an imaging probe (Model L14-5/38) operating at 6.6 MHz center frequency and having a RF data sampling rate of 20 MHz. The phantom was compressed and relaxed from the top by freehand motion using the transducer itself as a compression device. The saved RF frames were processed to obtain ASSE and analyzed as described later in the section.

2.2 In Vivo data

The data used in this work was chosen from our existing database of *in vivo* breast lesion cases that were acquired using freehand compression and had histopathological confirmation. The data were acquired at the University of Vermont by Brian Garra and his team using a Sonix-500RP scanner (Ultrasonix Medical, Richmond, BC, Canada) with an imaging probe (Model L14-5/38) operating at 10 MHz center frequency and having a RF data sampling rate of 40 MHz. The *in vivo* data acquisition was approved by the Institutional

Review Board and informed consent was obtained from the patients. The patients were instructed to hold breath during freehand compression and data acquisition. The depth of imaging ranged anywhere between 30mm to 56mm, depending on the location of the suspicious lesion. In all cases the lesion was positioned to lie approximately at the lateral symmetry of the image. Each patient dataset consisted of more than one acquisition cine-loop of RF frames. In total, the database consisted of 11 cancers and 11 benign lesions (excluding “fibrocystic changes”). However, only 7 benign and 9 malignant cases out of these total number of cases were included in this study. This is because only they contained at least one cine-loop where the sonogram captured a non-normal orientation of the long axis of the lesion with respect to axis of compression. Note that the data was originally acquired for a previous study on ASE and no effort was made at that time to find and capture data with lesion at non-normal orientation with respect to axis of compression. Fortunately, we still ended up having reasonable number of *in vivo* cases for this study because it is very challenging in reality to locate and retain perfectly geometrically symmetric lesion cross-section throughout the freehand acquisition.

2.3 ASSE formation

The effective applied compression between two consecutive frames in freehand elastography depends on the relationship between the freehand compression rate and the acquisition frame rate of the scanner (frames per second). We recently described an approach to dynamically pair RF frames such that the frame-average axial strain is around 1% (Xia and Thittai 2014). Briefly, this method treats the incoming frame as the post-compression frame and predicts the number of preceding frames that need to be skipped in order to locate a pre-compression frame, such that the ASE obtained from this pair will have a frame-average axial strain (FAAS) value of approximately 1%. The prediction is based on the FAAS values obtained in the previous frames saved in the buffer and the known acquisition frame rate. By this strategy the pre- and post-compression frames of the cine-loop are dynamically paired to result in ASE of similar image quality. Further details can be found in the reference. We used this method to select the appropriate frame-pairs and used it in a coarse-to-fine 2-D block-matching algorithm to obtain the axial displacement maps (Thittai et al. 2010). The cross-correlation lengths in the axial and lateral directions were set as 1.5 mm with a 60% overlap. ASSE was then estimated from the axial displacement using staggered strain estimator (Srinivasan et al. 2002, Thitaikumar et al. 2007).

2.4 Threshold Analysis

The cine-loop of RF data were processed (see description above) to obtain cine-loop of ASSEs. Each ASSE frame had an accompanying cross-correlation map from displacement tracking step and a frame-average axial strain value from corresponding ASE. Further, an estimate on the angle of deviation from the desired uniaxial compression of the transducer probe during freehand motion (for example, due to pressing the right side of the probe more than the left side), which can possibly result in poor quality uniaxial compression, was also available (Thittai et al. 2010a, Xia and Thittai 2014a). The importance of accounting for this inadvertent non-axial compression (or rotation/tilt) for correct interpretation of the ASSE was reported earlier (Thittai et al. 2010a). Only those ASSE frames from the cine-loop that had corresponding frame-average cross-correlation greater than or equal to 0.75,

corresponding frame average axial strain value within 0.5% to 2% range, and angle of deviation from uniaxial compression less than or equal to 5° were considered interpretable and analyzed further.

As noted in prior studies (c.f., Thitaikumar et al. 2007), the dynamic range of the ASSE image is influenced by a combination of factors, but most notably by applied axial strain, lesion-background modulus contrast, and the inclusion boundary condition – all of which are unknown *a priori*. Therefore, we normalized the pixels in ASSE by the estimated average-maximum axial-shear strain values near the lesion boundary, as described below (see figure 1).

Based on the outline of the lesion on the corresponding sonogram by one of the authors, a rectangular boxed region was initialized automatically. The dimensions of the rectangular ROI was such that it was 20% larger than the largest diameter of the lesion outline in the lateral direction and 20% larger than the largest radius in the axial direction. It was located on the top half of the lesion on the ASSE to find maximum-valued pixels. The pixels within this region that had corresponding correlation coefficient greater than or equal to 0.75 were sorted in descending order. In order to avoid possible erroneous peak value, we averaged the top 10 values to arrive at the maximum value to normalize the whole image. This method can be considered a self-normalizing technique where the ASSE features will be normalized for the applied axial strain and inherent elastic modulus contrast simultaneously. This method of normalization of ASSE is similar to that reported in Thittai et al. (2011).

We varied the segmentation threshold from 20% to 70% of the maximum ASSE value for each frame in the cine-loop of every data and computed the number of ASSE pixels within the lesion that was greater than or equal to this threshold value. A “*fill-in*” was considered to be demonstrated if at least 40% of the pixels within the lesion were greater than or equal to the segmentation threshold. This specific threshold value was chosen to define “*fill-in*” in order to be consistent with our previously reported work that used this feature (Xia and Thittai 2014a). All the key steps of the methods section are listed in the box chart shown in Box chart 1 below.

3. RESULTS

3.1 Tissue-mimicking Phantom Data

The effect of segmentation threshold on the number of frames that demonstrate a “*fill-in*” is plotted in figure 3 for the loosely-bonded and firmly-bonded inclusion phantom cases. It can be seen that the plot corresponding to the loosely-bonded inclusion phantom demonstrates “*fill-in*” in majority of the frames of the cine-loop over different segmentation thresholds. It must be noted that even at a high value of the segmentation threshold (at 70%) close to 50% of the frames still demonstrate this feature. On the other hand, only very few frames from firmly-bonded inclusion phantom demonstrate this feature even when the segmentation threshold value is close to the noise floor (at 20%). Figures 4 and 5 show an example frame of sonogram, corresponding ASE, and ASSE as a color overlay on sonogram at two different segmentation thresholds, for loosely-bonded and firmly-bonded inclusion phantoms, respectively.

3.2 In Vivo data

Figure 6 shows the effect of segmentation threshold on the number of frames that demonstrate a “*fill-in*” for the case of benign breast lesions. It must be noted that 7 of the 11 benign cases present in the database had at least 1 cine-loop that captured the lesion cross-section when its long-axis was non-normally oriented with respect to axis of compression and therefore analyzed and reported here. One can observe the same general trend in the feature value as a function of the segmentation threshold like that observed in the loosely-bonded inclusion phantom experiments. Figure 7 shows an example frame of sonogram, corresponding ASE, and ASSE as a color overlay on sonogram at two different segmentation thresholds for a benign breast lesion case.

Figure 8 shows the effect of segmentation threshold on the number of frames that demonstrate a “*fill-in*” for the case of malignant breast lesions. It must be noted that 9 of the 11 cancer cases in the database were analyzed and reported. One case did not have any prominent lesion appearance on the sonogram to outline and the other one seemed to have only very few RF frames saved. Therefore, we excluded these two cases from our analysis. It can be readily observed that the plots from several different cases seem to show a trend similar to that found in firmly-bonded phantom experiment. As the segmentation threshold is lowered (for e.g., at 20%) more frames start to demonstrate a “*fill-in*”. However, for thresholds greater than or equal to 40% the appearance of the “*fill-in*” diminishes rapidly. Figure 9 shows an example frame of sonogram, corresponding ASE, and ASSE as a color overlay on sonogram at two different segmentation thresholds for a malignant breast lesion case.

4. DISCUSSION

The results from phantom experiments shown in figure 3 suggest that the segmentation threshold can take any value in the range (0.3 to 0.8) and still demonstrate a “*fill-in*” only for the loosely-bonded inclusion and not for the firmly-bonded inclusion. However, in the case of *in vivo* breast lesion data the appropriate range of segmentation threshold value seems to be 0.4 to 0.6 (figures 6 and 8). It can be observed that for a segmentation threshold within this range all of the breast lesion cases reported can be correctly classified into benign and malignant, based on requiring a minimum % number of frames to demonstrate a “*fill-in*”. Although the database is not currently large enough to study the non-invasive classification performance using the “*fill-in*” feature from ASSE, it can be considered as a training set that has allowed in identifying appropriate segmentation threshold range. It is encouraging to note that the previous report (Thittai et al. 2011) on the use of NASSA feature for noninvasive breast lesion classification of 33 malignant and 30 benign cases, which was obtained using computer-controlled elastographic compression, showed promising results at a segmentation threshold of 0.5, which is within the range found in this study that analyzed the *fill-in* feature. This suggests that the same segmentation threshold range can be used to visualize and obtain the two different ASSE features.

It must be realized that we have plotted the % of total number of frames that demonstrate a “*fill-in*” at various segmentation thresholds, instead of analyzing a selected “typical” representative frame from each case. This was done deliberately so that the analysis avoids

subjective frame selection from a cine-loop. Further, this approach also makes the results less sensitive to the exact values used in the criteria for selection of interpretable ASSE frame. Note- each of the reported cases had at least 50 “interpretable” ASSE frames. The rationale behind this approach was that a *fill-in* due to the lesion boundary bonding condition will be observed in several ASSE frames only in the cine-loop of benign breast lesion case and not in the malignant case.

There is an important aspect regarding the image dynamic range in ASSE that is different when compared to ASE, although both images are derived from the same quasi-static compression. The ASE is usually displayed in a dynamic range based on some estimate of the applied axial strain. However, the dynamic range of the axial-shear strain values depend not only on the applied compression for a given inclusion-background modulus contrast, but also on the boundary bonding condition. Therefore, determining a dynamic range that will provide appropriate visualization of the region of interest in ASSE is very critical. Because the lesion and its boundary are of interest, we have used pixels close to the lesion boundary to determine the dynamic range of the image. The rectangular ROI we used had a width that was 20% larger than the lateral dimension of the lesion and a length that was 20% larger than half the axial dimension to ensure the maximum-valued pixel is not heavily influenced by the exactness of lesion outline, but at the same time it is due to the lesion boundary of interest and not from external boundary.

In reality, a more practical approach that would work for color-overlay of ASSE in real-time would be to allow the operator to provide a restricted rectangular ROI to include the lesion boundary of interest for determining maximum axial-shear strain value. The statistics of the pixel intensity within this ROI can be used to normalize and display the ASSE for the whole imaging frame.

5. CONCLUSIONS

The results demonstrate that in the case of *in vivo* breast lesion data the appropriate range for the segmentation threshold value seems to be 40% to 60%. It was noted that for a segmentation threshold within this range the entire breast lesion cases reported can be correctly classified into benign and malignant, based on requiring a minimum % of frames that demonstrated a “*fill-in*”.

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HIGHLIGHTS

- Effect of ASSE segmentation threshold on "*%fill-in*" feature computation was studied
- Data from tissue-mimicking phantom experiments were analyzed
- 16 *in vivo* breast lesion cases, acquired using freehand compression, were analyzed
- A segmentation threshold within the range of 40% to 60% was found be appropriate
- "*%fill-in*" thus computed has potential in non-invasive breast lesion classification

Figure 1.

An example frame of (a) sonogram (b) ASSE in default colorbar and (c) Normalized ASSE is shown. The user outline of the lesion appearance can be seen on sonogram. The rectangular region of interest used for obtaining the maximum-valued pixels from ASSE is shown in (b).

Figure 2.

All the key steps of the analysis method are listed in this box-chart for easy reading.

Figure 3. Plots showing the % of frames that demonstrate a “fill-in” at different segmentation thresholds for (left) loosely-bonded inclusion and (right) firmly-bonded inclusion phantoms.

Figure 4.

An example frame from loosely-bonded phantom data that shows the ASSE as a color overlay at two different segmentation thresholds- (top) 20% and (bottom) 50% .

Figure 5.

An example frame from firmly-bonded phantom data that shows the ASSE as a color overlay at two different segmentation thresholds- (top) 20% and (bottom) 50% .

Figure 6.

Plots showing the % of frames that demonstrate a "fill-in" at different segmentation thresholds for the benign breast lesion cases.

Figure 7.

An example frame from a benign breast lesion case (V0301) that shows the ASSE as a color overlay obtained at two different segmentation thresholds- (top) 20% and (bottom) 50% .

Figure 8.

Plots showing the % of frames that demonstrate a “fill-in” at different segmentation thresholds for the malignant breast lesion cases.

Figure 9.

An example frame from a malignant breast lesion case (V0306) that shows ASSE as a color overlay obtained at two different segmentation thresholds- (top) 20% and (bottom) 50%.