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An Adaptive Displacement Estimation Algorithm for Improved Reconstruction of Thermal Strain

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Abstract

Thermal strain imaging (TSI) can be used to differentiate between lipid and water-based tissues in atherosclerotic arteries. However, detecting small lipid pools *in vivo* requires accurate and robust displacement estimation over a wide range of displacement magnitudes. Phase-shift estimators such as Loupas' estimator and time-shift estimators like normalized cross-correlation (NXcorr) are commonly used to track tissue displacements. However, Loupas' estimator is limited by phase-wrapping and NXcorr performs poorly when the signal-to-noise ratio (SNR) is low. In this paper, we present an adaptive displacement estimation algorithm that combines both Loupas' estimator and NXcorr. We evaluated this algorithm using computer simulations and an *ex-vivo* human tissue sample. Using 1-D simulation studies, we showed that when the displacement magnitude induced by thermal strain was $>\lambda/8$ and the electronic system SNR was >25.5 dB, the NXcorr displacement estimate was less biased than the estimate found using Loupas' estimator. On the other hand, when the displacement magnitude was $\lambda/4$ and the electronic system SNR was >25.5 dB, Loupas' estimator had less variance than NXcorr. We used these findings to design an adaptive displacement estimation algorithm. Computer simulations of TSI using Field II showed that the adaptive displacement estimator was less biased than either Loupas' estimator or NXcorr. Strain reconstructed from the adaptive displacement estimates improved the strain SNR by 43.7–350% and the spatial accuracy by 1.2–23.0% ($p < 0.001$). An *ex-vivo* human tissue study provided results that were comparable to computer simulations. The results of this study showed that a novel displacement estimation algorithm, which combines two different displacement estimators, yielded improved displacement estimation and results in improved strain reconstruction.

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I. Introduction

Thermal strain imaging (TSI) is a ultrasound imaging modality that utilizes the relationship between sound speed and temperature as the basis for imaging contrast [1]–[6]. In water-based tissues near room and body temperature, the speed of sound increases with increasing temperature and the opposite is true for lipid-based tissues [7]. If a reference image is compared to an image taken after inducing a small temperature change ($\sim 2^\circ\text{C}$), water-based tissues appear to shift towards the transducer and vice-versa for lipid-based tissues. For temperature changes in this range, thermally induced mechanical expansion can be ignored and the shift between the reference and post-heating images can be considered to be solely the result of the temperature dependence of the speed of sound [4]. The derivative of this apparent displacement (“thermal strain”) can be used to differentiate between water and lipid-based tissues [8]. TSI-based detection of lipids has a number of potential medical applications including the identification of lipid pools in atherosclerotic plaques to assess plaque vulnerability [4], [9].

For TSI, the expression $\frac{\partial u}{\partial z} = -\beta \Delta T$ relates the derivative of the apparent displacement, u , in the direction of sound propagation (axial direction, z) to the change in temperature, T , through a material constant β [1], [4], [10]. The quantity $\frac{\partial u}{\partial z}$ is referred to as the “thermal strain”. Because TSI uses a small temperature change ($\sim 2^\circ\text{C}$), the induced thermal strain is relatively small ($\sim 1.0\%$) when compared to strains typically generated by ultrasound elastography imaging. However, small strains can still lead to large apparent displacements. In fact, when the temperature of a region that is several millimeters thick is increased by $1\text{--}2^\circ\text{C}$, a large dynamic range of displacement is generated ($0\text{--}50\text{ }\mu\text{m}$) with small displacements present near the top of the heated region and large displacements present near the bottom of the heated region.

Displacement estimation using ultrasound to track tissue motion and deformation has been well-studied in the literature and has led to a wealth of estimators and a rich analysis of the properties of these estimators. One of the earliest estimators that is still widely used is normalized cross-correlation (NXcorr) [11], [12]. Other groups have described modified versions of NXcorr that include phase-sensitive estimation and iterative temporal stretching in order to improve estimation accuracy and computational efficiency [13]–[15]. In addition to NXcorr, Loupas’ estimator and higher dimensional variations are also used to track tissue motion [16], [17]. Complementary studies have also been published that examine and compare the properties of many different estimators [18], [19]. Even more recently, novel algorithms that incorporate multi-level searches and Bayesian estimation approaches have been proposed [20]–[22].

However, in spite of the wide array of estimation algorithms, NXcorr and Loupas’ estimator remain widely used [23], [24]. NXcorr and Loupas’ estimator represent two fundamentally different formulations of the displacement estimation problem [25]. When estimation is formulated as a phase-shift estimation problem, it leads to a class of estimators commonly known as autocorrelation algorithms which include Kasai and Loupas’ estimator [16], [26]. On the other hand, when displacement estimation is posed as a time-shift estimation

problem, it can be shown that NXcorr, with appropriate filtering, is the maximum likelihood estimator [27].

We observed that, during TSI experiments, displacement tracking errors for time-shift and phase-shift estimators were localized to the top and bottom of the target, respectively. These tracking errors resulted in underestimation of the target dimensions in these regions when the strain was reconstructed from the displacement. We hypothesized that these errors happened because time-shift estimators improperly estimated small displacements and phase-shift estimators underestimated large displacements. This is further addressed in the Results (section IV) and Discussion (section V). One of the applications of TSI currently being investigated is the identification of lipid cores of atherosclerotic plaques in the carotid artery. Although carotid plaques are a target of great clinical interest, they are challenging to image because the typical carotid artery is 6.10 – 6.52 mm in diameter [28], [29]. This means that in a typically sized artery with 70% stenosis, the target plaque will have an area of only 20.4 – 23.4 mm². Furthermore, it is expected that the lipids within the plaque will be localized to a necrotic core which comprises only a small portion of the total plaque area [29]. Anatomical differences between patients may further complicate displacement tracking because the depth of the artery will vary from patient to patient [30]. The thermal strain in the artery is linearly proportional to T and β which implies that the measured displacement is proportional to the integral of these quantities. Thus, a lipid pool within a carotid plaque will experience a range of displacements that depends upon its relative position within the heating beam.

Although a median filter or another similar filter can be used to increase the SNR and potentially alleviate some of these issues, aggressive filtering can result in the loss of small spatial details and does not help to recover a phase-wrapped signal. The observed differences in the performance of Loupas' estimator and NXcorr, coupled with the challenges related to imaging carotid plaques, motivated the development of a new adaptive displacement estimation algorithm that would have robust performance over a large range of displacements. The goal of this adaptive displacement estimation algorithm was to provide more accurate displacement estimates that would result in thermal strain reconstructions with improved strain SNR and spatial accuracy.

In this study, we examined the properties of the Loupas' estimator and NXcorr over a range of displacements and noise levels that were typically observed during TSI of atherosclerotic plaques using computer simulations. Using these results, we created an adaptive estimation algorithm that combined estimates from Loupas' estimator and NXcorr. We showed that this adaptive estimation algorithm provided superior performance when compared to either Loupas' estimator or NXcorr alone. Finally, we applied the algorithm to an *ex-vivo* amputated femoral artery of a human subject. The potential application of this adaptive estimation algorithm in other areas of ultrasound imaging is also briefly discussed.

II. Materials and Methods

A. Conventional Displacement Estimation

Displacement estimation was conducted using Loupas' estimator and NXcorr. Unless otherwise specified, the axial kernel for displacement calculations was $128 \mu\text{m}$ or 1.8λ . Loupas' estimate for displacement was calculated as in [18]. Loupas' estimator calculates displacement based off of the quadrature demodulated data or IQ data and can be expressed as

$$u = \frac{c}{4\pi f_c} \frac{\text{atan} \left(\frac{\sum_{m=0}^{M-1} \sum_{n=0}^{N-2} [Q(m,n)I(m,n+1) - I(m,n)Q(m,n+1)]}{\sum_{m=0}^{M-1} \sum_{n=0}^{N-2} [I(m,n)I(m,n+1) + Q(m,n)Q(m,n+1)]} \right)}{1 + \text{atan} \left(\frac{\sum_{m=0}^{M-1} \sum_{n=0}^{N-2} [Q(m,n)I(m+1,n) - I(m,n)Q(m+1,n)]}{\sum_{m=0}^{M-1} \sum_{n=0}^{N-2} [I(m,n)I(m+1,n) + Q(m,n)Q(m+1,n)]} \right) / 2\pi}, \quad (1)$$

where c is the speed of sound and f_c is the center frequency. M and N represent the axial and temporal extent, respectively, over which the displacement is calculated. I and Q represent the in-phase and quadrature components of the signal, respectively. The numerator calculates the average phase difference between a reference and shifted signal. When the four-quadrant inverse tangent function is used to calculate the phase difference, the result is bounded by $\pm\pi$ which corresponds to displacements on the range of $\pm\lambda/2$. Because medical ultrasound relies on the two-way propagation time, the maximum displacement that can be estimated is effectively bounded by $\pm\lambda/4$. The denominator is a frequency normalization term to account for local variations in the center frequency. For a more thorough analysis of Loupas' estimator, the reader is referred to [16], [18].

NXcorr calculates the displacement by finding the lag between a reference and shifted signal at which the correlation coefficient is maximized. For 1-D NXcorr, this can be expressed as

$$u = \frac{c}{2f_s} \arg \max_{\tau} \frac{\sum_{i=-M/2}^{M/2} y_0^*(i) y_1(i+\tau)}{\sum_{i=-M/2}^{M/2} [y_0(i)]^2 \sum_{i=-M/2}^{M/2} [y_1(i+\tau)]^2}, \quad (2)$$

where f_s is the sampling frequency of the system, y_0 is the reference signal, y_1 is the shifted signal, and $*$ represents the complex conjugate. Here, the signals are assumed to be complex numbers formed from the IQ data such that $y = I + jQ$. Typical ultrasound scanners use a sampling frequency of 40 MHz which does not yield sufficient displacement resolution to track the displacements generated in low strains scenarios. As a result, the data set is typically upsampled. In order to further improve the displacement resolution, the peak of the cross correlation function is typically calculated using interpolation. These procedures yield displacement estimates with sub-micron quantization error. However, it should be noted that the quantization error is not typically the limiting factor for modern displacement estimation in ultrasound imaging. For a more thorough analysis of NXcorr, the reader is referred to [18], [27].

For 1-D NXcorr, the IQ data was upsampled to 420 MHz. The cross-correlation coefficient was calculated from the magnitude of the baseband signal and the peak of the cross-

correlation coefficient was estimated using parabolic interpolation. 1-D NXcorr was used to estimate displacement for all simulation data. 2-D NXcorr was implemented to account for small lateral displacements observed during *ex-vivo* experiments that likely resulted from vibrations in the room. The lateral kernel size for 2-D displacement calculations was 0.32 mm or three A-lines. For 2-D NXcorr, the IQ data was upsampled to 420 MHz axially and the final displacement estimate was calculated using 2-D parabolic interpolation.

B. Ultrasound Radiofrequency (RF) 1-D Data Simulation

We conducted 1-D ultrasound simulations to verify our empirical observation that Loupas' estimator and NXcorr performed differently depending on the magnitude of displacement being tracked. In addition, we expanded the investigation to include the performance of these estimators for a wide range of scatterer densities and noise levels. The RF pulse was simulated with a center frequency of 21 MHz and a 50% bandwidth which corresponded to the specifications of the linear array transducer (MS250, FUJIFILM, Visualsonics Inc, Canada) used in *ex-vivo* experiments. The RF data was synthesized to simulate a line of scatterers experiencing a constant strain of 0.05% over 55 mm. This resulted in a linear displacement ramp with a displacement range from 0 μm to 27.5 μm . This range of displacement extends beyond the phase-wrapping limit ($\lambda/4$) for Loupas' estimator and is a good representation of displacements found in TSI. The received echo signal for the reference and shifted signals were simulated according to the following model:

$$r(t) = [x(t) * s(t)] + n(t).$$

$x(t)$: Gaussian enveloped RF pulse
 $s(t)$: scatterer distribution
 $n(t)$: White Gaussian system noise
 $r(t)$: received RF signal

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$r(t)$: received RF signal

Scatterer positions were drawn from a uniform distribution and the amplitude of the scatterers was drawn from a normal distribution. The scatterer density was varied from 0.37 – 11.0 scatterers per -3 dB width of the enveloped RF pulse. These scatterer densities correspond to calculated scatterer SNR (sSNR) of 0.79 – 1.83. Additive, white Gaussian noise was used to simulate electronic system noise present in real imaging systems. The electronic SNR (eSNR) ranged from 8.6 – 50.4 dB which corresponded to the range of SNR found in typical ultrasound systems. The received RF signal was converted to IQ data and saved with a sampling frequency of 40 MHz in order to mimic the signal processing found in typical commercial ultrasound scanners. The displacement was calculated for these simulated lines of scatterers using both Loupas' estimator and 1-D NXcorr. This process was repeated for 1000 independent scatterer realizations. Tissue attenuation of ultrasound was not accounted for in these simulations, but was incorporated into Field II simulations of TSI (section II. D) [31].

To evaluate the properties of the estimators, we defined the percent bias as:

$$\% \text{ bias} = \frac{u_{True} - E[u_{Est}]}{u_{True}} \times 100, \quad (4)$$

where u_{True} represents the true displacement, u_{Est} represents the displacement estimated using either Loupas or NXcorr, and $E[\cdot]$ represents the expectation operator. The coefficient of variation (COV) was also calculated and was defined as:

$$COV = 20 \log_{10} \frac{\sigma_{Est}}{u_{True}}. \quad (5)$$

Here, σ_{Est} represents the sample standard deviation of the estimated displacements. The COV of the Cramer-Rao lower bound (CRLB) was also calculated using the formulation in reference [32]. The results of these metrics were plotted as a function of simulated displacement magnitude in order to derive thresholds which specified the optimal performance regions for Loupas' estimator and NXcorr. The corresponding levels of eSNR and sSNR were also stored for future use with the adaptive displacement estimation algorithm.

C. Adaptive Displacement Estimation Algorithm

Based on the simulation results, an algorithm was designed to minimize the percent bias and COV. Fig. 1 is a flowchart outlining the steps in the adaptive estimation algorithm which are described in more detail below:

Step 1)—We computed the displacement estimate using both NXcorr (u_{NXcorr}) and Loupas' estimator (u_{Loupas}) separately and used these estimates to compute an estimate for u_{True} , the true displacement. Unlike simulations, the true displacement is not known in real imaging scenarios. For this reason, we computed the mean displacement (u_{mean}) at every position (z_i) between the two algorithms as an estimate for u_{True} :

$$u_{mean}(z_i) = \frac{u_{Loupas}(z_i) + u_{NXcorr}(z_i)}{2}. \quad (6)$$

Step 2)—If Loupas' estimate and the NXcorr estimate were both within $\pm 50\%$ of u_{mean} at a given z_i , then we considered the two algorithms to be in agreement. Empirically, it was found that the bias and variance in Loupas' estimate and NXcorr often resulted in estimates that were within $\pm 30\%$ of u_{mean} in the absence of phase-wrapping or peak-hopping errors. In the presence of phase-wrapping or peak-hopping, the difference in the estimates relative to u_{mean} was often in excess of $\pm 100\%$. A threshold of $\pm 50\%$ was chosen empirically in order to take into account these factors and because the accuracy of u_{mean} as an estimate for u_{True} was unknown.

If in agreement: Step 3)—The eSNR and sSNR were estimated by acquiring a series of conventional B-mode frames. Let $I_j(x, y)$ be the IQ data for the j th frame collected prior to

heating. If we assume that the electronic system noise is additive white Gaussian noise, then the temporal average $\bar{I}(x, y) = \frac{1}{N} \sum_{j=1}^N I_j(x, y)$ is a good estimate of the true value of the IQ data in the absence of electronic noise when the number of frames, N , is large. The eSNR can then be calculated as:

$$eSNR(x, y) = 20 \log \frac{\bar{I}(x, y)}{\sqrt{\frac{1}{N-1} \sum_{j=1}^N (I_j(x, y) - \bar{I}(x, y))^2}} \quad (7)$$

The sSNR can also be estimated as:

$$sSNR(x, y) = \frac{\frac{1}{x_0 y_0} \sum_{j=y}^{y+y_0} \sum_{i=x}^{x+x_0} \bar{I}(i, j)}{\sqrt{\frac{1}{x_0 y_0 - 1} \sum_{j=1}^N (I_j(x, y) - \bar{I}(x, y))^2}}, \quad (8)$$

which is the ratio of the mean and the standard deviation of (x, y) in a local spatial kernel with dimensions x_0 by y_0 .

The calculated values of eSNR and sSNR were used to choose two appropriate displacement thresholds from the stored simulation data. One threshold was derived using the percent bias metric and the other was derived from the COV metric. If u_{mean} was below both of these displacement thresholds, then the Loupas estimate was used. The NXcorr estimate was used if u_{mean} was greater than both of these thresholds. However, if u_{mean} lay somewhere between the two displacement thresholds, then a weighted estimate, u_{weight} , was generated:

$$u_{weight} = (1 - \alpha) u_{Loupas} + \alpha u_{NXcorr}, \quad (9)$$

where $\alpha = \frac{|u_{mean}| - |u_{Th, Loupas}|}{|u_{Th, NXcorr}| - |u_{Th, Loupas}|}$ is a measure for the relative distance of μ_{mean} from the two thresholds. Here, $u_{Th, Loupas}$ corresponds to the threshold which is the smaller of the percent bias or COV threshold. $u_{Th, NXcorr}$ corresponds to the threshold which is the larger of the percent bias or COV threshold. Thus, α has a value that always ranges from zero to one. When α is zero, the final estimate is equal to the estimate from Loupas' estimator. From there, α changes linearly as a function of u_{mean} until it is equal to one and the final estimate is equal to the displacement estimate from NXcorr.

If not in agreement: Step 3)—If the two algorithms did not agree, it was likely because of other errors. Peak-hopping errors can occur with both Loupas' estimator and NXcorr whereas a phase-wrapping error is unique to phase-based estimators like Loupas' estimator. Typically, displacement estimates change smoothly along the axial dimension. However, in the case of a peak-hopping error, there is an interruption in this smooth change. By utilizing this observation, peak-hopping errors could be detected by computing and comparing the standard deviation of the Loupas and NXcorr estimates within a 50 μm region about z_i . A large increase in the standard deviation in one algorithm that was not present in the other

indicated a peak-hopping error. Otherwise a phase-wrapping error was likely and the NXcorr estimate was chosen.

D. Simulation of Thermal Strain Imaging

A region 30 mm (axial) $\times$ 14 mm (lateral) $\times$ 4 mm (elevation) was populated with 50,000 randomly generated scatterers in order to generate a reference configuration prior to heating. A cylindrical target with a radius of 3 mm was centered at 22 mm axially. Scatterers in this region had a mean signal strength that was 40 dB greater than the background. The material constant β was chosen to $-0.4 \text{ }^\circ\text{C}^{-1}$ for the cylindrical target and zero for the background. The temperature rise, T , was set to be 1°C which corresponded to a maximum displacement of 24 μm . The values of β and T were chosen so that the simulated displacements mimicked values typically seen in tissue [4]. The temperature change was assumed to be uniform across the target. A second configuration that corresponds to the speckle distribution after heating was generated by shifting the scatterers according to these specifications.

Field II, a linear acoustic simulation package, was used to simulate imaging with a linear array transducer (MS250, FUJIFILM, Visualsonics Inc, Canada) [31]. The center frequency for the transducer was set to be 21 MHz with a 50% bandwidth. The B-mode transmit and receive foci were set to 23 mm and used an F/2 configuration. The Field II data was stored with a sampling frequency of 40 MHz in order to mimic commercial ultrasound scanners. All other Field II simulation parameters were consistent with the specifications of the MS250 provided by the manufacturer. The ultrasound attenuation coefficient was set to 0.5 dB/cm/MHz. After generating images with Field II, white Gaussian noise was added to the image of the reference configuration to generate 30 reference images for use with the adaptive algorithm. The same noise was also added to the image of the post-heating configuration. The SNR for these images was set to 35 dB. These data were used as the input for Loupas' estimator, 1-D NXcorr, and the adaptive estimation algorithm. In order to compare the performance of the adaptive algorithm with median filtering, displacement estimates were also filtered where noted. A 2-D median filter was applied in the axial direction. A kernel length of $55 \times 135 \mu\text{m}$ or 3×3 pixels (axial $\times$ lateral) was used. The derivative of displacement along the axial direction was calculated using a first order Savitzky-Golay filter with a 1.0 mm kernel length to estimate thermal strain.

The entire simulation procedure outlined in this section was repeated for 25 randomly generated scatterer distributions. The percent error is defined as the absolute value of the percent bias (equation 2). The target size was defined as the area within the target with $>0\%$ strain. For a single speckle realization, the strain SNR was calculated to be

$$SNR_{strain} = \frac{\bar{s}_{target}}{\sigma_{target}}, \quad (7)$$

Where $\bar{s}_{target}$ is the mean strain within the target and σ_{target} is the standard deviation of the strain within the target. Differences in target size and strain SNR were evaluated using

Tukey's range test for multiple comparisons. Differences with p-values <0.001 were considered to be significant.

E. Ex-vivo Human Amputation Specimen and Thermal Strain Imaging

The femoral artery and the surrounding neurovascular bundle from an above-knee amputation were obtained under Internal Review Board consent approved at the University of Pittsburgh. The specimen was embedded in a gelatin background which was fabricated by combining gelatin (G-2500, Sigma Aldrich Corp., St. Louis, MO), water, and ultrasound scatterers (1% cellulose by wt, S3504, Sigma Aldrich Corp., St. Louis, MO) [33]. The specimen was placed in the liquid gelatin matrix and the gelatin was allowed to cool and solidify.

The specimen was simultaneously imaged and heated using the MS250 with a custom heating transducer that provided a broad heating beam [34]. The MS250 was stabilized with a mechanical arm. The heating transducer was composed of six elements that were attached to the imaging transducer through a plastic manifold and were geometrically focused such that energy was deposited from approximately 20–30 mm axially in an $8 \text{ mm} \times 2 \text{ mm}$ (lateral $\times$ elevational) tissue volume that was centered in the imaging plane. Prior to heating, 30 consecutive reference frames were captured to calculate eSNR and sSNR for use with the adaptive displacement estimation algorithm. Then, heating pulses and imaging pulses were interleaved with the heating transducer being driven with a 56% duty cycle and the imaging being conducted at 10 Hz. Imaging was conducted at 21 MHz and IQ data was sampled at 40 MHz and saved for offline processing.

Displacement was estimated using Loupas' estimator, 2-D NXcorr, and the adaptive estimation algorithm as described in section II.A and II.C. 2-D NXcorr was used in order to compensate for small lateral displacements that were present due to vibrations in the room. Only axial displacements from 2-D NXcorr were used in the adaptive algorithm. The thermal strain was calculated using a first order Savitzky-Golay filter with a 1.5 mm kernel length. The strain in regions with B-mode signal amplitudes smaller than 50 dB was ignored because the B-mode signal in this region was too poor to provide meaningful displacement estimates. The small signal amplitude likely resulted from tissue attenuation. All aforementioned computational tasks were implemented and performed in MATLAB R2013b (Mathworks Inc., MA) on an Intel i7-2600 3.40 GHz quad-core (Intel Corp., CA) machine with 12 gigabytes of memory. After imaging, Oil Red O histology was performed to identify regions with lipids [35].

IV. Results

The percent bias for several levels of eSNR and sSNR are shown in Fig. 2. Fig. 2 demonstrates that Loupas' estimator produced less biased estimates than NXcorr when the displacement was small and in imaging situations with low eSNR and sSNR. We found that the performance of NXcorr increased with increasing eSNR, sSNR, and displacement magnitude. Fig. 2 also shows that for a given eSNR and sSNR, there exists a displacement magnitude above which NXcorr estimates are less biased than Loupas' estimates. In general, it was found that for an eSNR ≥ 25.5 dB and a displacement magnitude $\geq \lambda/8$, Loupas'

estimator was less biased than NXcorr. Conversely, when the eSNR was >25.5 dB and the displacement magnitude was $>\lambda/8$, NXcorr was less biased than Loupas' estimator. These data are presented graphically in Fig. 4a.

Fig. 3 shows that similar trends are observed for the performance of Loupas' estimator and NXcorr when the COV is evaluated. Loupas' estimator produces estimates with smaller variance than NXcorr for small displacements, low eSNR, and low sSNR. The thresholds based on the COV corresponding to optimal ranges for Loupas' estimator and NXcorr are presented graphically in Fig. 4b. Fig. 4b shows that Loupas' estimator has better performance for a wider range of noise levels and displacements when the COV metric is used as compared to the percent bias metric. However, NXcorr rapidly becomes the preferred estimator for medium and high SNR. In general, we found that the COV was smaller for Loupas' estimator when the eSNR was <25.5 dB and the displacement magnitude was $<\lambda/4$. Conversely, when the eSNR was >25.5 dB and the displacement magnitude was $>\lambda/4$, NXcorr had smaller variance than Loupas' estimator.

In order to estimate eSNR and sSNR in real imaging situations, we used the procedure outlined in section II.C. Panel a) in Fig. 5 shows the percent bias for the IQ data as a function of imaging depth after averaging different numbers of frames. Panel b) of Fig. 5 shows the average root mean square error per pixel for IQ data as a function of number of frames averaged. In both cases, the average of 100 frames was considered to be the "true" value. From these plots, it can be seen that after averaging more than 30 frames, there is little benefit in continued averaging. These data sets served as the rationale for using 30 frames to calculate eSNR and sSNR.

The top row of images in Fig. 6 show displacement estimates for a single simulated speckle realization. The displacement images have been cropped and overlaid on the B-mode image to show only the displacement in the region where β was non-zero. This region corresponds to the true location and size of the inclusion. The corresponding strain images are shown in the second row.

In the top row of images in Fig. 7, the average percent displacement error is shown for each algorithm. The average percent displacement error is shown for the filtered displacement estimates in the second row of images. Strain was calculated as described in section II.D for both the unfiltered and filtered displacement estimates. The calculated target size is shown for unfiltered and filtered versions of each algorithm in Fig. 7g. All possible pairs are significantly different ($p < 0.001$) in Fig. 7g. Similarly, the strain SNR for each algorithm is shown in Fig. 7h. The strain SNR is significantly different for all possible pairs ($p < 0.001$) except between the A-NXF and L-LF pairs.

Fig. 8 shows thermal strain images of an *ex-vivo* arterial specimen embedded in gelatin, corresponding Oil red O histology, and a gross image of the specimen. Approximately the entire region that is displayed was insonified with the heating transducer. In the B-mode image in Fig 8a, there is a hyperechoic layer that is surrounded by a hypoechoic interior. Oil red O staining in Fig. 8c shows that this layer corresponds to a layer of bright red staining that is consistent with adventitial fat that surrounding the femoral artery. These observations

are further supported by gross images of the vessel in Fig. 8f where the artery is buried in a sheath of pale, yellow, adventitial fat. All of the thermal strain images confirm that the hyperechoic layer was fatty and surrounded a core of water-based tissue. The black arrows point to deposits of fat that were identified in thermal strain reconstructions from all three algorithms. The strain SNR in the region indicated by the solid arrow was 1.77, 1.11, 2.03 for Loupas' estimator, NXcorr, and adaptive estimator respectively. The strain SNR in the region indicated by the dashed arrow was 3.04, 2.12, 3.25 for Loupas' estimator, NXcorr, and adaptive estimator respectively.

V. Discussion

Fig. 6a shows that the B-mode image overestimated the size of the inclusion. This is a direct result of the point spread function of the transducer. In addition, panel d), shows that Loupas' estimator underestimated large displacements. This is consistent with the theory underlying a phase-based estimator (equation 1) as well as simulation data in Fig 2. Large displacements beyond the phase-wrapping threshold were confined to the lower portion of the target (Fig 6a). This is because the thermal strain is the derivative of the apparent displacement. As such, constant thermal strain yields a linear displacement ramp which serves to localize small and large displacements to the top and bottom of the target, respectively. NXcorr and the adaptive algorithm did not suffer from phase-wrapping and the displacement estimates near the bottom of the target in Fig 6b and 6c have less error than the corresponding region in the target tracked by Loupas' estimator (Fig 6d). This result is more apparent in Fig 7a, 7b, and 7c which show the mean displacement error across 25 speckle realizations. Fig. 6h shows that strain calculated from Loupas' estimator results in underestimation of the lesion only near the bottom of the lesion. As expected, Fig. 6f and 6g show that the strain calculated from the adaptive and NXcorr displacement estimates does not suffer from this error.

Fig. 7c shows that, on average, the error in Loupas' estimator was localized to a thin rim near the top of the target and a larger region near the bottom of the target. This trend agrees with the data that was presented in Fig. 1 in which the bias in Loupas is highest when the displacement is less than one micron or greater than the phase wrapping threshold. Fig. 7b demonstrates that the error in NXcorr is localized to regions near the top of the target with small displacements. This effect was masked in Fig. 6b due to the choice of the dynamic range, but follows the same trend as the data shown in Fig. 1. Furthermore, Fig. 6a shows that the overall error from the adaptive algorithm is the minimum combination of error from NXcorr and Loupas' estimator.

The second row of images in Fig. 7 demonstrates that median filtering can be used to further decrease the displacement error. Fig. 7g and 7h demonstrate that strain calculated from the filtered, adaptive algorithm (AF) provided a 1.2 – 23.0% improvement in spatial accuracy and a 43.7 – 350% improvement in strain SNR as compared to the strain calculated from the filtered and unfiltered NXcorr (NXF, NX) and Loupas estimates (LF, L). The filtered version of the adaptive algorithm (AF) provided the best spatial accuracy and strain SNR (Fig 7g and 7h). In most cases, as might be expected, the median filtered versions of the displacement estimates provided significantly better results than the unfiltered versions. The

difference in the strain SNR between the filtered and unfiltered version of Loupas' estimator was not significant at the $p < 0.001$ level but was significant if this threshold was relaxed to $p < 0.05$. It is important to note that although the adaptive algorithm was shown to perform better than Loupas' estimator or NXcorr individually, we expect that the exact degree of improvement will depend on the range of displacement being tracked as well as the eSNR and sSNR.

These simulation results were consistent with the *ex-vivo* data presented in Fig. 8. Fig. 8e, 8f, and 8g, show that the adaptive algorithm provided the best strain SNR within the adventitial layer. A comparison of Fig. 8e, 8f, and 8g shows that the lower edge of the fatty deposit indicated by the solid black error is missing from Fig. 8e. This region was near the bottom of the adventitial layer and experienced large displacements close to or beyond the phase-wrapping threshold. As a result, Loupas' estimator underestimated the displacement in this region which resulted in an incorrect strain estimate. The strain reconstruction from the adaptive algorithm (Fig. 8f) appeared to provide the best reconstruction of this region.

The CRLB is the smallest possible variance that an unbiased estimator can achieve and it predicts that the variance in the estimate should increase with increasing displacement magnitude due to signal decorrelation [32]. We quantified the variance in the estimate using the COV which was found to decrease as a function of increasing displacement magnitude. However, the *absolute* magnitude of the variance (data not shown) increased with increasing displacement magnitude which was consistent with the prediction from the CRLB and [32]. In this study, we presented bias and variance as quantities normalized to the displacement magnitude because, the relative error in the estimate is more important than the absolute error for strain estimation.

Previous studies have examined the performance of Loupas' estimator and NXcorr in response to a number of different variables including, eSNR and displacement magnitude [18]. Pinton *et al.*'s simulations applied a constant displacement and imaged with a center frequency of 5 MHz. Pinton *et al.*, found that when the true displacement was small ($\sim \lambda/12$) and the eSNR was extremely low (6 dB), Loupas' estimator was less biased than NXcorr. However, this result was not generalized to other eSNR. In addition, the effects of sSNR on the respective algorithms were not studied. The simulations presented in this study were designed to mimic TSI in which strain is more likely to be constant within a given tissue type. Furthermore, our study used a center frequency of 21 MHz which corresponded to the center frequency for the ultrasound transducer used in *ex-vivo* experiments (MS250). These factors might account for some of the differences in results seen between this study and previous studies.

One limitation of this study was that the simulation experiments used to derive the displacement thresholds for the adaptive algorithm assumed a simplistic 1-D model for ultrasonic tracking. Palmeri *et al.* investigated ultrasonic tracking of acoustic radiation force induced displacements [36]. They showed that a number of parameters including tracking frequency, transducer bandwidth, and elevational focusing could affect the bias and variance of displacement estimates. A 1-D simulation experiment does not account for transducer focusing in the lateral and elevational directions. Despite neglecting these factors, the results

presented showed that the adaptive algorithm performed better than Loupas' estimator and NXcorr.

The adaptive estimation algorithm presented does not rely solely on changes in signal processing. It also requires the acquisition of a series of reference frames in order to calculate image statistics. In this implementation, 30 reference frames were used to calculate these statistics. Assuming a typical clinical imaging depth of 50 mm and an ultrasound array transducer with 128 beams, this corresponds to an imaging time of 265 ms. Furthermore, when displacement is estimated for clinical use, it is often necessary to design motion compensation algorithms to account for transducer motion and physiologic motion [37], [38]. Oftentimes, these algorithms rely on the acquisition of number of reference frames to track and subsequently remove confounding motion [39]–[41]. Given the relatively small increase in total acquisition time and the added utility of these frames for motion compensation, it is unlikely that the acquisition of these frames will greatly impede the utility of this novel adaptive estimation algorithm.

Another key concern is related to the safety of actively heating tissue. AIUM standards state that a 2°C temperature change can be sustained for more than 50 hours without significant, adverse, biological effects [42]. However, it is still desirable to limit the total energy being delivered due to the difficulty of accurately predicting the temperature change *in-vivo*. The adaptive displacement estimation algorithm presented might serve as one means of addressing this concern because it is able to exploit the sensitivity of Loupas' estimator in detecting small displacements while side-stepping the issue of phase-wrapping that becomes an even greater issue at higher frequencies. Maximizing the sensitivity and accuracy of estimation algorithms is one means of minimizing the amount of energy that needs to be delivered to tissue. Going forward, one of the most important applications of this adaptive estimation algorithm might be for use with TSI in the carotid artery.

The adaptive estimation algorithm presented here is unique in that it selects the appropriate estimator based on the properties of the estimators and the image statistics. It exploits the fact that the performance of displacement estimators depends on the conditions under which they operate and that no single estimator is likely to achieve good performance over a full range of conditions typically encountered. It is able to compensate for errors in one estimator by switching to the alternate estimator. For example, if the displacement is larger than the phase-wrapping threshold, then the NXcorr estimate is used in place of the erroneous Loupas estimate. Since the estimator properties that govern this switching are pre-calculated and stored, the overall added computation time for steps specific to the adaptive algorithm is minimal. For the adaptive algorithm, the total computation time was found to be 2.2 hours for a data set containing 1528 axial points and 512 lines. It was found that approximately 98.6% of the total computation time was spent calculating the NXcorr estimate, less than 0.1% of the time was spent calculating Loupas' estimate, and 1.4% of the time was spent on steps specific to the adaptive algorithm.

Although this algorithm was found to be useful for TSI, it could also be used for other applications. New applications would require a series of simulations to study the properties of the estimators being used under different noise conditions and under the appropriate

ultrasonic operation conditions. For example, after repeating the simulation studies using the appropriate transducer center frequency and bandwidth, this algorithm could be translated to improve the estimates of tissue strain in ultrasound elastography techniques where the mechanical strains of interest are relatively small and a significant portion of the displacement lies in the range of optimal performance for Loupas' estimator. Applications that require displacement tracking with high frequency transducers would benefit from this approach because at higher frequencies the phase-wrapping limit of Loupas' estimator becomes more problematic. One application for which this algorithm might be suitable is intravascular acoustic radiation force imaging [43].

Although the adaptive estimator is able to circumvent errors in one estimator by using another estimator, it is still possible that both Loupas' estimator and NXcorr might simultaneously provide incorrect estimates. This situation might occur most often when the displacement is larger than the phase-wrapping threshold and NXcorr experiences a peak-hopping error. If this occurred it would be difficult to recover a good estimate of the true displacement using the current adaptive approach. In this case, however, the adaptive algorithm should have the same performance as either Loupas' estimator or NXcorr individually. In this situation, previous studies have shown that it might still be possible to achieve a good estimate of the strain by applying techniques like Kalman filtering [44].

Although this algorithm was developed using Loupas' estimator and NXcorr, the underlying principle for this algorithm could be utilized with any pair of estimators. Thus, another approach to correct errors in this adaptive algorithm might be to use displacement estimation algorithms incorporating priors in place of NXcorr [45]–[47]. These algorithms have been shown to have robust performance for large strains up to 10% and to reduce speckle decorrelation noise. Combining these estimators with Loupas' estimator might provide robust displacement and strain estimation over a larger dynamic range. The field of view of TSI is currently limited by the size of the heated region. As this issue is addressed and the thickness of the heated region increases, an adaptive estimator incorporating prior knowledge might be used to further improve the dynamic range of displacement estimates. Adaptive estimation with priors might also be useful for vascular elastographic applications where the displacement and strain vary markedly from systole to diastole. Using the adaptive algorithm, the appropriate estimator would naturally be chosen in systole and diastole on the basis of the observed displacement. Furthermore, an improved estimate of vascular mechanical strain might also be helpful for TSI when a time series analysis approach is used to estimate the thermal strain [38]. In addition to extending this adaptive algorithm, future work should also include a comparison of the adaptive algorithm and other higher order displacement estimation techniques including Bayesian speckle tracking, dynamic programming approaches, and estimation techniques based on the monogenic signal [17], [20], [45]. This comparison would provide a more complete understanding of the strengths and weaknesses of each technique.

VI. Conclusions

We showed that when the displacement magnitude induced by thermal strain imaging was $>\lambda/8$ and the electronic system SNR was >25.5 dB, the displacement estimate obtained from

normalized cross-correlation was less biased than the estimate found using Loupas' estimator. On the other hand, when the displacement magnitude was $\lambda/4$ and the electronic system SNR was 25.5 dB, Loupas' estimator had less variance than normalized cross-correlation. We also demonstrated the feasibility of applying these results to create an adaptive displacement estimation algorithm and showed using Field II simulations that this algorithm resulted in strain reconstructions with improved strain SNR and spatial accuracy. The adaptive algorithm was also applied to thermal strain imaging of an *ex-vivo* human amputation sample with comparable results. The results from this study warrant further investigation of this adaptive algorithm through an *in-vivo* study.

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Figure 1.
Flow chart describing the adaptive displacement estimation algorithm

Figure 2.

Percent bias as a function of displacement for the Loupas and NXcorr. Rows represent different levels of eSNR. Columns represent different sSNR. The horizontal black lines represent 0% and 10% bias. The vertical dashed line represents $\lambda/4$ displacement.

Figure 3.

The coefficient of variation as a function of displacement for the Loupas, Nxcorr, and the CRLB. Rows represent different levels of eSNR. Columns represent different sSNR. The vertical dashed line represents $\lambda/4$ displacement.

Figure 4.

Performance maps for Loupas and NXcorr. a) and b) The true displacement at which Loupas' estimator and NXcorr have equal percentage bias and percentage variance respectively is plotted as a surface for different values of eSNR and sSNR. The space below the surfaces indicates the region in which estimates from Loupas either have less percentage bias or percentage variance than NXcorr and vice versa for the space above the surface.

Figure 5.

Effect of averaging on IQ data: a) indicates the % bias as a function of depth after averaging different numbers of B-mode frames. b) indicates the average RMS error per pixel between the # of frames averaged and the “true” value. Error bars represent the standard deviation of the RMS error across all pixels in a single frame. In both plots, the average of 100 frames was considered to be the “true” value when calculating % bias.

Figure 6.

Displacement and TSI images for one set of computer simulations. TSI was simulated using Field II to image a cylindrical inclusion with $\beta = -0.4 \% \text{ } ^\circ\text{C}^{-1}$ and where a one degree uniform temperature change was assumed. The 2nd, 3rd, and 4th columns show results from adaptive algorithm, NXcorr, and Loupas respectively. The true displacement and strain are overlaid on the B-mode image in panels a) and e) respectively. The strain and displacement within the inclusion were cropped and overlaid on the B-mode image

Figure 7.

Displacement error and strain results from 25 simulated speckle realizations. The first row of images is the average displacement error calculated from the unfiltered displacement estimates. The second row of images is the average displacement error calculated from median filtered displacement estimates. Strain was calculated from the displacement estimates. Plots g) and h) are box and whisker plots of the target size and strain SNR. Error bars represent the interquartile range and '+' indicate outliers. A, NX, and L designate data where unfiltered displacements were calculated using the adaptive, Nxcorr, and Loupas' estimator respectively. An 'F' indicates the median filtered version of that algorithm. The true target size was 28.3 mm². All possible pairs in g) are significantly different ($p < 0.001$). In h), all pairs are significantly different except the A-NXF and L-LF pairs ($p < 0.001$).

Figure 8.

B-mode, TSI-B-mode overlay, and Oil red O histology for an ex vivo amputation sample in panels a), b), and c) respectively. In c), bright red staining indicates regions with lipids. A gross image of the specimen is shown in d). Thermal strain was calculated from displacement estimated using Loupas, 2D XCorr, and the adaptive algorithm in panels d), e), and f) respectively. The dynamic range for the strain images is $\pm 1.0\%$ strain. The heated region corresponds to the entire region being shown. The strain in regions where the B-mode intensity was < 50 dB was masked in b), d), e), and f). The black arrows indicate a layer of adventitial fat at the top of the tissue.