Published in final edited form as:

Ultrason Imaging. 2015 October ; 37(4): 277–293. doi:10.1177/0161734614561128.

A PDE-based Regularization Algorithm toward Reducing Speckle Tracking Noise: A Feasibility Study for Ultrasound Breast Elastography

Li Guo^{1,2,3}, Yan Xu³, Zhengfu Xu¹, and Jingfeng Jiang¹

¹Department of Mathematical Sciences, Michigan Technological University

²Department of Biomedical Engineering, Michigan Technological University

³Department of Mathematical Sciences, University of Science and Technology of China

Abstract

Obtaining accurate ultrasonically-estimated displacements along both axial (parallel to the acoustic beam) and lateral (perpendicular to the beam) directions is an important task for various clinical elastography applications (*e.g.* modulus reconstruction and temperature imaging). In this study, a partial differential equation (PDE)-based regularization algorithm was proposed to enhance motion tracking accuracy. More specifically, the proposed PDE-based algorithm, utilizing two-dimensional displacement estimates from a conventional elastography system, attempted to iteratively reduce noise contained in the original displacement estimates by mathematical regularization. In this study, the physical constraint used by the above-mentioned mathematical regularization was tissue incompressibility.

This proposed algorithm was tested using computer-simulated data, a tissue-mimicking phantom and *in vivo* breast lesion data. Computer simulation results showed that the method significantly improved the accuracy of lateral tracking (*e.g.* 17X at 0.5% compression). From *in vivo* breast lesion data investigated, we have found that, as compared to the conventional method, higher quality axial and lateral strain images (*e.g.* at least 78% improvements among the estimated contrast-to-noise ratios of lateral strain images) were obtained. Our initial results demonstrated that this conceptually and computationally simple method could be useful to improve the image quality for ultrasound elastography with current clinical equipment as a post-processing tool.

Keywords

ultrasound; elastography; speckle tracking; strain imaging; de-noising

I. Introduction

Ultrasound-based quasi-static elastography¹⁻³ is a surrogate for manual palpation to assess variations in tissue elasticity. In recent reports, good outcomes of non-invasive

Address all correspondence to: Jingfeng Jiang, PhD, Material and Mineral Engineering Building 309, Department of Biomedical Engineering, Michigan Technological University, Houghton, MI 49931, **Voice:** (906)-487-1943, **Fax:** (906)-487-1717, jjjiang1@mtu.edu.

differentiation benign breast tumors from malignant breast cancers were achieved by several independent clinical studies⁴⁻⁶. The clinical potential of this technique for management of other neoplasms and cardiovascular diseases, including monitoring thermal ablation for liver tumors^{7, 8}, characterizing thyroid lesions^{9, 10}, imaging vascular plaques¹¹ and, assessing the age of deep vein thrombosis¹², has also been reported.

Using nearly unmodified clinical equipment, tissue elasticity information can be readily estimated from radio frequency (RF) data acquired using clinical ultrasound transducers by obtaining an RF echo frame, deforming the tissue, obtaining another RF frame, and then tracking displacements that occurred between those two frames of RF data. The axial displacement field is then used to calculate the component of strain along the direction of the acoustic beam (hereafter referred as to axial strain) to form an axial strain image. This axial strain image is interpreted as an image of the reciprocal of the shear or Young's moduli of the tissue¹ assuming an uniform stress distribution. In typical systems, displacements perpendicular/lateral to the ultrasound beam that are necessary for accurate motion tracking are not retained because of their low quality. However, in several applications, accurate lateral displacement estimation is important because all components of the displacement vector field and/or their spatial derivatives are required not only for interpretation of the tissue elasticity information but also for further advanced processing. For instance, in cardiac elasticity imaging, hearts often exhibit complex 3D motion. Consequently, the exclusion of non-axial information could introduce angle-dependent artifacts¹³. Furthermore, both components of the displacement fields are needed for estimation of shear strains^{14, 15}, temperature distributions through measuring thermal expansions^{16, 17}, and reconstruction of modulus distributions through mathematical inversions¹⁸⁻²⁰.

Previous research efforts for improving estimation of non-axial motion have been well documented both in the literature of ultrasound blood flow imaging and elasticity imaging. A displacement estimation method developed by Techavipoo et al.²¹ used radiofrequency echo data along multiple angular insonification directions of the ultrasound beam. This approach is known as "angular compounding"²¹. Jensen²² and Anderson²³ have independently improved the estimation of non-axial blood velocity components by introducing non-axial oscillations/modulations in their respective imaging point spread functions. While these two methods could be highly accurate, both methods require significant modifications (*e.g.* rapid beam steering or special beam-forming) of current medical ultrasound systems.

On the other hand, several methods have been developed to work with conventional ultrasound echo data^{14, 24-27}. Among them, a few methods have demonstrated that coupling (either explicitly or implicitly) axial and lateral displacement estimations could significantly improve displacement estimation for both directions. Lateral displacements can be explicitly tied to relevant axial displacements by assuming that tissues being imaged are incompressible²⁴. Konofagou and Ophir²⁸ proposed a sub-sample estimation approach where axial and lateral displacements can be iteratively improved by re-correlating ultrasound echo signals through instantaneous motion compensations. In recent work by Brisseau et al.²⁷, they first mathematically formalized local 2D motion/deformations as affine transformations and then jointly solved all parameters including axial and lateral

translations (*i.e.* rigid-body motion) using constrained nonlinear programming. Ebbini²⁶ elegantly proved that, in the vicinity of the true correlation peak between the pre- and post-deformation ultrasound echo signals, magnitude vectors of the correlation function are orthogonal to their zero-phase contours. This observation has led to a novel 2D search method to simultaneously determine sub-sample displacements. Viola and Walker have extended their initial 1D spline-based motion tracking method²⁹ to track motion in multi-dimensions³⁰. Since this extension enables them to simultaneously solve the axial and lateral displacements, their work nicely fits into the category of coupled speckle tracking.

Our objective of this study was to develop an alternative method to improve lateral speckle tracking using conventional ultrasound echo data acquired by clinical equipment. The rest of the paper is structured as follows. In Section II, using original displacement estimates obtained from a conventional speckle tracking algorithm³¹, the proposed PDE-based de-noising algorithm was formulated by applying one additional constraint: tissue incompressibility. Enforcement of tissue incompressibility is appropriate for compression breast elastography because breast tissues are water-based. To demonstrate its feasibility, the proposed algorithm was further validated using computer-simulated RF echo signals³², data acquired from a tissue-mimicking gelatin phantom³³ and *in vivo* breast tissue data³ in Section III, followed by Discussions in Section IV and Conclusions in Section V.

II. Materials and Methods

A. Theoretical Background

In breast elastography, ultrasonically-measured displacement fields are often corrupted by measurement noise. In order to reduce noise contained in these raw displacement estimates, we formulated a novel partial differential equation (PDE)-based de-noising algorithm to enforce tissue incompressibility assumption. This tissue incompressibility assumption is based on the hydrated nature of the biological tissues and the incompressibility of fluids³⁴.

Given $\tilde{d} = (\tilde{u}, \tilde{v})$ measured by ultrasound speckle tracking³¹ from a regular domain Ω , obtaining a “regularized” vector field $d = (u, v)$ on Ω is equivalent to solving the following an optimization problem,

$$\min_{u,v} F(u, v) \quad F(u, v) = \int_{\Omega} \left(\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} \right)^2 d\Omega + \lambda_1 \int_{\Omega} (\tilde{u} - u)^2 d\Omega + \lambda_2 \int_{\Omega} (\tilde{v} - v)^2 d\Omega \quad (1)$$

where λ_1 and λ_2 are two positive constants. In the right hand side of Eqn. (1), the first item is the calculated incompressibility from the regularized displacement vector field under the plane strain assumption, and the second and third items are fidelity terms of the measured lateral (perpendicular to the acoustic beam direction) and axial (parallel to the acoustic beam direction) displacements, respectively. The regularization parameters λ_1 and λ_2 control the trade-off between the fidelity and the degree of tissue incompressibility. Optimization of Eqn. (1) was first based on the classic Euler-Lagrange equation³⁵ and then a finite difference method was used to iteratively solve for the “regularized” displacement field $d = (u, v)$. More details can be found below in Section B and in the Appendix below.

B. Implementation of the Proposed De-noising Algorithm

As illustrated in Fig. 1, the proposed de-noising algorithm consisted of two steps: (1) estimating the initial displacement field $\tilde{d} = (\tilde{u}, \tilde{v})$ using a conventional speckle tracking method³¹, (2) using the proposed PDE method to obtain the “regularized” displacement field $d = (u, v)$ by a numerically optimization process of Eqn. (1).

In the first step, a quality-guide block matching (QBM) method³¹ was used to obtain initial displacement vectors covering a rectilinear grid (*i.e.* an approximately 2 cm by 2 cm rectangular region of interest [ROI]). Similar to the classic block-matching algorithm, the QBM algorithm was also designed to match patterns in the pre-deformation RF echo frame with patterns in the post-deformation RF echo frame using finite-sized search kernels. However, the adopted QBM algorithm first created a short list of high quality displacement estimates in a coarse grid, and then used these high quality displacement estimates to guide subsequent speckle tracking using a predictive search strategy³⁶. The density of displacement estimation slightly varied but approximately on the order of 0.2 (axial) mm $\times$ 0.5 mm.

In the second step, the ultrasonically-measured displacement vector field from Step 1 was first resampled onto a (denser) 0.1 mm $\times$ 0.1 mm grid. Starting from this resampled displacement vector field $\tilde{d} = (\tilde{u}, \tilde{v})$, the proposed algorithm iteratively updated the “regularized” displacement vector field $d = (u, v)$ for each point within the ROI, so that Eqn. (1) is minimized as follows:

1. Subdivide the domain (2D imaging plane) into a set of uniform grid points where the initial displacement estimates $\tilde{d} = (\tilde{u}, \tilde{v})$ is available for each and every grid point.
2. Update the regularized displacement estimates $d = (u, v)$ following the proposed finite difference scheme (*i.e.* Eqns. A(7) and A(9) in the Appendix).
3. For each iteration n , compare these regularized displacements d^n with regularized displacements d^{n-1} from previous iteration $n-1$. The criterion for convergence was set with a pre-determined threshold ε such that, $\|d^n - d^{n-1}\| < \varepsilon$. $\|\cdot\|$ is a standard L2 norm and ε was 10^{-13} .

Details for updating the regularized displacements $d = (u, v)$ using the finite difference numerical scheme have been included in Appendix for completeness. In the iterative process described above, units for displacements in Eqn. (1) were mm. The regularization parameters λ_1 and λ_2 were empirically chosen. λ_1 was approximately 0.1 while λ_2 was approximately 10. The ratio between them was approximately 100, reflecting the ratio of error variances between axial and lateral displacements. In the literature, statistical methods³⁷, such as generalized cross validation (GCV) or L-curve, may be used to determine appropriate λ_1 and λ_2 . Nevertheless, these methods do not guarantee optimal *regularization parameters*, as shown in the simple example illustrated by Vogel³⁷.

C. Strain Estimation

The axial, lateral and shear strains were estimated using the following equations once the final axial and lateral displacements, u and v , were obtained as described in Section II-B above,

$$\epsilon_y = \frac{\partial v}{\partial y} \quad (2)$$

$$\epsilon_x = \frac{\partial u}{\partial x} \quad (3)$$

In this study, we estimated local strains using a regularized numerical differentiation method described by Chartrand³⁸.

D. Experimental Validation

The proposed PDE-based de-noising algorithm was validated using computer-synthesized data, tissue-mimicking phantom data and *in vivo* breast tissue data. The first test was to estimate error variances of the displacement estimation using simulated pre- and post-deformation RF echo signals. These computer-simulated data were created using finite element (FE) simulations with different levels of additive noise. The errors of axial and lateral displacements were calculated after the proposed de-noising algorithm had been applied.

In the second test, one of four spherical targets (10mm diameter) in a tissue mimicking (TM) gelatin phantom (10 cm × 10 cm × 10 cm)³³ was used to demonstrate effectiveness of the proposed algorithm in a controlled setting. The spherical target was approximately four times stiffer than the background and was separated from other three targets to avoid strain concentration artifacts induced by closely-spaced targets. RF echo data were acquired using a Siemens SONOLINE(tm) Antares (Siemens Medical Solutions Inc., Mountain View, CA) equipped with a multi-row linear array transducer (VFX9-4) sampling at 40 MHz and the AXIUS Direct Ultrasound Research Interface (URI) software package³⁹. The ultrasound transducer was pulsed at 8.89 MHz. The transducer was centered in a compression plate (a 17 cm square) and mounted in a laboratory fixture which manually compressed the phantom to obtain frame-average strains of roughly 1.5%. Hereafter, we will refer the phantom experiment as Case P.

The third test compared performance of the proposed algorithm to the QBM method using *in vivo* breast tissue data. From an archived database of ultrasound scans of human breast lesions, 2 RF echo data sets (one benign fibroadenoma and one invasive ductal carcinoma) were arbitrarily chosen. *In vivo* freehand breast ultrasound examinations were performed by clinicians using identical equipment (*i.e.* Siemens SONOLINE Elegra ultrasound scanners equipped with high frequency linear array transducers [VFX13-5], Siemens Healthcare USA Inc., Mountain View, CA) for both patients. The detailed protocol for data acquisition can be found in Hall et al.³

E. Data Analysis

Two metrics were chosen to assess the performance of the proposed de-noising algorithm. The first metric was the normalized cross correlation among the pre-deformation and motion-compensated post-deformation RF echo fields (a measure of motion tracking accuracy applied to the entire region of interest). By applying the displacement estimates to the deformed data and remapping to the coordinates of the pre-deformation data, we registered two RF echo fields with apparent deformations. A higher NCC value between two registered echo fields implied that the apparent deformation between these two ultrasound fields was more accurately compensated. Therefore, the displacement estimates were more accurate. Hereafter the first metric will be referred as to motion tracking accuracy that was normalized between 0 and 1.

The second metric was the weighted contrast-to-noise ratio (CNR) ⁴⁰ :

$$CNR = \frac{|I_t - I_b|}{(w_t \sigma_t^2 + w_b \sigma_b^2)^{1/2}} \quad (5)$$

where I and σ^2 denoted means and variances of signals, and subscripts b and t represented the background and target, respectively. To calculate the CNR using Eqn. (4) for each strain image, we used the manually-segmented lesion (representing the ‘target’) and the rest of strain image (representing the ‘background’). The manual segmentation was done for each axial strain image. w was a weighting of the area of the target and the background to the total area given by $w_x = \text{area}_x / \text{area}_{\text{total}}$. The inclusion of the weighted area was necessary because the target and the background contribute differently to the noise estimates ⁴⁰.

All numerical experiments were done off-line using a Windows-based dual-CPU (1.8-GHz) workstation (DELL Precision 3600, DELL Inc., TX, USA) equipped with 16-Gbytes of memory. The PDE-based algorithm was implemented in FORTRAN using an INTEL compiler, whereas other data analysis calculations were all done in MATLAB (Mathworks Inc., MA, USA)..

III. Results

A. Numerical Phantom Results

In this test, a numerical phantom (4 cm × 4 cm) was constructed. The phantom contained a target whose diameter was 1 cm and whose stiffness was 5 times stiffer than that of the background. Using a commercially-available FEA software package (ANSYS version 12.0, ANSYS Inc., PA, USA), the numerical phantom was uni-axially compressed in a range from 0.1-5%. Different levels of additive Gaussian noise were added to FEA-simulated displacements to generate simulated speckle tracking results, *i.e.* ultrasonically measured displacements. The processed PDE-based algorithm was applied to these simulated speckle tracking results to verify the performance of the proposed de-noising algorithm. Results shown in **Fig. 2(a)-(b)** and **Table 1** below were estimated using approximately 1000 statistically independent realizations. It is clear that, from **Fig. 2(a)-(b)**, the proposed method significantly reduced lateral noise (up to 17X lower), whereas it also reduced noise in the axial displacements for small strains (<=1%). We also found that the means of the

remaining displacement errors were nearly zeroes ($<10^{-4}$ mm), suggesting that this proposed PDE-based method didn't induce biases during the de-noising processing.

B. Results from TM Phantom Data

As shown in Fig. 3 below, even in a laboratory environment for Case P, the lateral displacement image (Fig. 3(d)) of the QBM algorithm contained significant noise. Consequently, the spherical target was invisible in the resultant lateral strain image (Fig. 3(h)). However, the proposed method improved the lateral displacement estimates and the subsequent lateral strain image (see Fig. 3(i)).

C. Results from In vivo Breast Tissue Data

To demonstrate effects of reducing speckle tracking noise, we also selected one benign fibroadenoma (Case B) and one malignant invasive ductal carcinoma (Case M). Cases B and M are shown in Figs. 4 and 5, respectively. In both cases, the breast tissues were compressed by approximately (frame-averaged strain) 1.5%.

In case B, Fig. 4(b)-(i) compared (axial and lateral strains, and axial and lateral displacements) results estimated by the proposed de-noising method with those of the QBM method³¹. The general appearance of the axial and lateral displacement images (Figs. 4(c) and 4(e)) processed by the proposed de-noising method was smoother as compared to results from the QBM algorithm (Figs. 4(b) and 4(d)). It is interesting to note that the lateral displacement image in Fig. 4(e) seemed more consistent with the tissue landmarks visible in the B-mode image (Fig. 4(a)), *i.e.* the gross appearance of the lesion and tissue interfaces around it.

In case B, a “slipping” interface resulted in large “banding” artifacts (see arrows in Figs. 4(f), 4(g) and 4(i)) due to fairly complex interfacial tissue motion near the breast tumor boundary. The phenomenon was more pronounced in Figs. 4(g) and 4(i) once noise in images has been mitigated, as compared to the axial strain image from the QBM (Fig. 4(f)). This is consistent with the high CNR values obtained from the proposed de-noising algorithm (see Table 2).

In case M, the proposed algorithm also improved the smoothness of both axial and lateral displacement estimates (Fig. 5(b) vs. Fig. 5(c) and Fig. 5(d) vs. Fig. 5(e)), resulting in less noisy axial and lateral strain images (Fig. 5(f) vs. Fig. 5(g) and Fig. 5(h) vs. Fig. 5(i)). Some “slipping” boundaries were apparent at the adipose and fibro-glandular tissue interfaces. It is worth noting that the general appearance of the breast tumor was clearly visible in the lateral strain image (Fig. 5(i)) processed by the proposed de-noising method, whereas there was no identifiable target on the original lateral strain image (Fig. 5(h)). This was consistent with the estimated CNR_l values summarized in Table 2 below.

All three estimated metrics of these three cases (Cases P, B and M), namely, motion tracking accuracy, CNR_a and CNR_l , are summarized in Table 2 below.

IV. Discussion

The adoption of the quality-guided block-matching (QBM) algorithm³¹ was largely due to the fact that this QBM algorithm can reduce the occurrence of large tracking errors due to “false correlation peaks”⁴¹. Large displacement errors may cause potential problems during estimation of gradients and therefore are not desirable for the subsequent mathematical regularization. More details of this method are published in³¹. It is worth noting that the selection of this quality-guided speckle tracking is for our convenience. Other speckle tracking algorithms that are capable of providing initial displacement estimates could be readily used.

Using computer-simulations, it is easy to see (**Table 1**) that the proposed de-noising method didn't improve the axial displacement estimates once the compression exceeded 1.5%, whereas it continued to improve the lateral displacement estimates. This early simulation result suggested that the proposed method may be better suited for small compressions such as 0.5-1%. More parametric studies with *in vivo* breast data are still ongoing.

We have quantitatively demonstrated that the proposed PDE-based de-noising method can improve CNR_l values of lateral strain imaging (78%, 290% and 700% for Cases P, B and M, respectively, as suggested by **Table 2**). The CNR_a values for three cases were also slightly improved (1%, 8% and 37% for Cases P, B and M, respectively, as suggested by **Table 2**). This finding is consistent with the results of computer simulations where the enhancements for the lateral displacements were greater as compared to enhancements among axial displacements. It is interesting to note that accuracy of motion tracking (ρ_{TT}) was actually reduced or unchanged. This is understandable because improving the signal coherence between the pre- and motion-compensated post-deformation echo signals was not a part of the formulation used by the proposed study. In other words, using motion continuity or compressibility may penalize the restoration of signal coherence. This stipulation is consistent with ideas used by other publications^{27, 31}.

Recently, the use of the axial shear strain data alone has shown its values in the differentiation of benign breast lesions from malignant breast tumors⁴². However, to fully quantify “shearing” as a surrogate of tissue connectivity around a breast lesion being imaged, contributions from the lateral shear strain cannot be ignored for many circumstances. Although it is yet to demonstrate the clinical use of the full shear strain imaging, the proposed improvement for lateral displacement estimation could lead to full shear strain data using conventional ultrasound echo data. Our future research will explore how this method will add values to clinical studies involving in shear strain imaging.

We used the tissue incompressibility as a means to reduce noise in the lateral displacement estimates. In Eqn. (1), the formulation implied that the plane strain assumption was adopted in the initial feasibility study. We understood that 2D ultrasound data does not satisfy either plane stress condition or plane strain condition⁴³. This topic is a subject of future investigations.

For a displacement vector field consisting of 100 by 100 displacement estimates, the un-optimized FORTRAN code took approximately 12 minutes to complete the de-noising

process. If we further reduce the threshold ε (see Section II(B)) to 10^{-9} , which is adequate for practical imaging applications, the time needed to complete those calculations mentioned above will be reduced to 5 minutes. With strategies such as code optimization, parallelization and a multi-grid method, it is possible to implement the proposed algorithm onto a high end clinical scanner as an on-line post-process algorithm that can finish a case in 30 seconds.

In this work, we described options we have chosen and gave justifications for those choices to reduce speckle tracking noise. While we believe that they are good choices, the methodology represents, however, only an alternative to other previously described methods. This initial feasibility study is encouraging and we believe that the method warrants further clinical studies to explore its full clinical utility. We think further testing of this algorithm may be done in conjunction with elastic modulus reconstruction methods¹⁸⁻²⁰. It is well recognized that the outcome of a modulus inversion method is heavily dependent on the quality of the displacement estimation, because the displacement function is the fundamental input being utilized to solve distributions of elastic material properties of the tissue being imaged¹⁹.

V. Conclusions

A novel PDE-based de-noising algorithm was presented. Computer simulation results showed that the method greatly (up to a factor of 17 for 0.5%) improved the accuracy of lateral tracking. Initial results also suggest that the proposed algorithm may be better suited for small (e.g. 0.5-1%) compressions, given the fact that the proposed method may penalize the axial displacement estimates at large (>1.5%) compressions. From *in vivo* breast lesion data investigated, we found high quality lateral displacements and lateral strains can be estimated. In particular, our results showed that the proposed method can significantly (at least 78%) improve the contrast-to-noise ratios among estimated lateral strain images in three cases investigated. Our initial results demonstrated that this conceptually and computationally simple method could be used to improve displacements for ultrasound-based quasi-static elasticity imaging with current clinical equipment. In the near future, we plan to further investigate the use of this algorithm in conjunction with more advanced elasticity imaging techniques such as modulus inversion⁴⁴ and shear strain imaging.

Acknowledgment

We also thank our colleagues at University of Wisconsin-Madison (especially Prof. Timothy Hall of Medical Physics) and the Charing Cross Hospital (London, United Kingdom) for providing breast data used in this study. This study is partially funded by the a grant from NIH (R15-CA179409-01A1) and the start-up funds from Michigan Tech University. Y. Xu is supported by NSFC grants (No.11371342 and No.11031007) and funding from Fok Ying Tung Education Foundation (No.131003).

Appendix Solution of the Optimization Problem

Given $\tilde{d} = (\tilde{u}, \tilde{v})$ measured by ultrasound speckle tracking³¹ from a regular domain Ω , obtaining a regularized vector field $d = (u, v)$ on Ω is equivalent to solving the following an optimization problem,

$$\min_{u,v} F(u,v) \quad F(u,v) = \int_{\Omega} \left(\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} \right)^2 d\Omega + \lambda_1 \int_{\Omega} (\tilde{u} - u)^2 d\Omega + \lambda_2 \int_{\Omega} (\tilde{v} - v)^2 d\Omega \quad (\text{A1})$$

where λ_1 and λ_2 are two positive constants. In the right hand side of Eqn. (A1), the first item is the calculated incompressibility from the regularized displacement vector field, and the second and third items are fidelity terms of the measured lateral (perpendicular to the acoustic beam direction) and axial (parallel to the acoustic beam direction) displacements, respectively. The regularization parameters λ_1 and λ_2 control the trade-off between the fidelity and the degree of incompressibility. The Euler-Lagrange variation of $F(u,v)$ (Eqn. (A1)) can be written as follows,

$$-u_{xx} - v_{yy} + \lambda_1 (\tilde{u} - u) = 0 \quad \text{in } \Omega \quad (\text{A2})$$

$$-v_{yy} - u_{xy} + \lambda_2 (\tilde{v} - v) = 0 \quad \text{in } \Omega \quad (\text{A3})$$

Utilizing the gradient-descent method⁴⁵, together with a Neumann boundary condition (*i.e.* Eqn. (A6)), yields the following PDEs after adding an artificial time variable t ,

$$u_t - u_{xx} - v_{yy} + \lambda_1 (\tilde{u} - u) = 0 \quad \text{in } \Omega \quad (\text{A4})$$

$$v_t - v_{yy} - u_{xy} + \lambda_2 (\tilde{v} - v) = 0 \quad \text{in } \Omega \quad (\text{A5})$$

$$\nabla d \cdot s = 0 \quad \text{at } \partial\Omega \quad (\text{A6})$$

In Eqn. (A6), s is the outward normal at the boundary $\partial\Omega$. The purpose of Eqn. (A6) is to extend the first-order continuity in the regularized displacement field $d=(u,v)$ beyond the boundary $\partial\Omega$.

Eqns. (A4)-(A6) can be solved numerically using a standard finite difference scheme on a rectilinear grid $\Omega = [a, b] \times [c, e]$. The space was divided into uniform meshes such as, $a = x_0, x_1, x_2, \dots, x_{nx} = b$ and $c = y_0, y_1, y_2, \dots, y_{ny} = e$. More specifically, the numerical scheme used to approximate the (pseudo) temporal and spatial derivatives reads as follows,

$$\frac{u_{i,j}^{n+1} - u_{i,j}^n}{\Delta t} = \frac{u_{i-1,j}^n - 2u_{i,j}^n + u_{i+1,j}^n}{\Delta x^2} + \frac{v_{i+1,j+1} - v_{i+1,j-1} - v_{i-1,j+1} + v_{i-1,j-1}}{4\Delta x\Delta y} - \lambda_1 (u_{i,j} - \tilde{u}_{i,j}^n) \quad (\text{A7})$$

$$\frac{v_{i,j}^{n+1} - v_{i,j}^n}{\Delta t} = \frac{v_{i-1,j}^n - 2v_{i,j}^n + v_{i+1,j}^n}{\Delta y^2} + \frac{u_{i+1,j+1} - u_{i+1,j-1} - u_{i-1,j+1} + u_{i-1,j-1}}{4\Delta x\Delta y} - \lambda_2 (v_{i,j} - \tilde{v}_{i,j}^n) \quad (\text{A8})$$

where $i = 1, 2, \dots, nx - 1$ and $j = 1, 2, \dots, ny - 1$.

In Eqns. (A7) and (A8), subscripts denote spatial locations, while superscripts denote (pseudo) time. For instance, $u_{i,j}^n$ denotes the function value of u at a grid point (x_i, y_j) that is evaluated at $t = n \cdot \Delta t$. The grid spacing can be determined as follows: $\Delta x = (b - a)/nx$ in the

lateral direction and $y = (e - c)/ny$ in the axial direction. Simple bilinear interpolations were used to re-sample the original ultrasonically-measured displacements (approximately 0.2×0.5 mm) to a denser grid (i.e. approximately 0.1×0.1 mm). The chosen time step Δt satisfies with $\frac{2\Delta t}{\Delta x^2} + \frac{2\Delta t}{\Delta y^2} \leq k \leq 1$ to ensure the numerical stability, where k is a small constant.

The iterative process (Eqns. (A7) and (A8)) starts with the following initial conditions:

$$u_{i,j}^0 = \tilde{u}_{i,j} \quad (\text{A9})$$

$$v_{i,j}^0 = \tilde{v}_{i,j} \quad (\text{A10})$$

The iterative process terminates if $\|d^{n+1} - d^n\| \leq 10^{-13}$. All numerical experiments successfully converged within less than 50,000 iterations.

Some ghost grid points are needed to estimate gradients of u and v at the spatial boundaries Ω . Mirror “boundary” conditions at Ω are used as follows,

$$u_{-1,j} = u_{1,j} \quad \text{and} \quad v_{-1,j} = v_{1,j} \quad (\text{A11})$$

$$u_{nx+1,j} = u_{nx-1,j} \quad \text{and} \quad v_{nx+1,j} = v_{nx-1,j} \quad (\text{A12})$$

$$u_{i,-1} = u_{i,1} \quad \text{and} \quad v_{i,-1} = v_{i,1} \quad (\text{A13})$$

$$u_{i,ny+1} = u_{i,ny-1} \quad \text{and} \quad v_{i,ny+1} = v_{i,ny-1} \quad (\text{A14})$$

In Eqns. (A11)-(A14), all ghost grid points are in the left hand sides of equations.

References

1. Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrasonic Imaging*. 1991; 13:111–34. [PubMed: 1858217]
2. O'Donnell M, Skovoroda AR, Shapo BM, Emelianov SY. Internal displacement and strain imaging using ultrasonic speckle tracking. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*. 1994; 41:314–25.
3. Hall TJ, Zhu Y, Spalding CS. In vivo real-time freehand palpation imaging. *Ultrasound in Medicine & Biology*. 2003; 29:427–35. [PubMed: 12706194]
4. Itoh A, Ueno E, Tohno E, et al. Breast disease: clinical application of US elastography for diagnosis. *Radiology*. 2006; 239:341–50. [PubMed: 16484352]
5. Regner DM, Hesley GK, Hangiandreou NJ, et al. Breast lesions: evaluation with US strain imaging—clinical experience of multiple observers. *Radiology*. 2006; 238:425–37. [PubMed: 16436810]
6. Burnside ES, Hall TJ, Sommer AM, et al. Differentiating benign from malignant solid breast masses with US strain imaging. *Radiology*. 2007; 245:401–10. [PubMed: 17940302]
7. Kolokythas O, Gauthier T, Fernandez AT, et al. Ultrasound-based elastography: a novel approach to assess radio frequency ablation of liver masses performed with expandable ablation probes: a feasibility study. *J Ultrasound Med*. 2008; 27:935–46. [PubMed: 18499853]

8. Rubert N, Bharat S, DeWall RJ, et al. Electrode displacement strain imaging of thermally-ablated liver tissue in an in vivo animal model. *Med Phys.* 2010; 37:1075–82. [PubMed: 20384243]
9. Rago T, Santini F, Scutari M, Pinchera A, Vitti P. Elastography: new developments in ultrasound for predicting malignancy in thyroid nodules. *J Clin Endocrinol Metab.* 2007; 92:2917–22. [PubMed: 17535993]
10. Bae U, Dighe M, Dubinsky T, Minoshima S, Shamdasani V, Kim Y. Ultrasound thyroid elastography using carotid artery pulsation: preliminary study. *J Ultrasound Med.* 2007; 26:797–805. [PubMed: 17526611]
11. Cespedes EI, de Korte CL, van der Steen AF, von Birgelen C, Lancee CT. Intravascular elastography: principles and potentials. *Seminars in Interventional Cardiology.* 1997; 2:55–62. [PubMed: 9546985]
12. Xie H, Kim K, Aglyamov SR, et al. Staging deep venous thrombosis using ultrasound elasticity imaging: Animal model. *Ultrasound in Medicine and Biology.* 2004; 30:1385–96. [PubMed: 15582239]
13. Zervantonakis IK, Fung-Kee-Fung SD, Lee WN, Konofagou EE. A novel, view-independent method for strain mapping in myocardial elastography: eliminating angle and centroid dependence. *Phys Med Biol.* 2007; 52:4063–80. [PubMed: 17664595]
14. Konofagou E, Ophir J. A new elastographic method for estimation and imaging of lateral displacements, lateral strains, corrected axial strains and Poisson's ratios in tissues. *Ultrasound in Medicine & Biology.* 1998; 24:1183–99. [PubMed: 9833588]
15. Rao M, Varghese T, Madsen EL. Shear strain imaging using shear deformations. *Med Phys.* 2008; 35:412–23. [PubMed: 18383661]
16. Simon C, Vanbaren P, Ebbini ES. Two-dimensional temperature estimation using diagnostic ultrasound. *IEEE Trans Ultrason Ferroelectr Freq Control.* 1998; 45:1088–99. [PubMed: 18244264]
17. Miller NR, Bamber JC, ter Haar GR. Imaging of temperature-induced echo strain: preliminary in vitro study to assess feasibility for guiding focused ultrasound surgery. *Ultrasound in Medicine & Biology.* 2004; 30:345–56. [PubMed: 15063516]
18. Kallel F, Bertrand M. Tissue elasticity reconstruction using linear perturbation method. *IEEE Transactions on Medical Imaging.* 1996; 15:299–313. [PubMed: 18215911]
19. Zhu Y, Hall TJ, Jiang J. A finite-element approach for Young's modulus reconstruction. *IEEE Transactions on Medical Imaging.* 2003; 22:890–901. [PubMed: 12906243]
20. Oberai AA, Gokhale NH, Doyley MM, Bamber JC. Evaluation of the adjoint equation based algorithm for elasticity imaging. *Physics in Medicine & Biology.* 2004; 49:2955–74. [PubMed: 15285258]
21. Techavipoo U, Chen Q, Varghese T, Zagzebski JA. Estimation of displacement vectors and strain tensors in elastography using angular insonifications. *IEEE Transactions on Medical Imaging.* 2004; 23:1479–89. [PubMed: 15575406]
22. Jensen JA, Munk P. A new method for estimation of velocity vectors. *IEEE Trans Ultrason Ferroelectr Freq Control.* 1998; 45:837–51. [PubMed: 18244236]
23. Anderson ME. Multi-dimensional velocity estimation with ultrasound using spatial quadrature. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control.* 1998; 45:852–61.
24. Lubinski MA, Emelianov SY, Raghavan KR, Yagle AE, Skovoroda AR, O'Donnell M. Lateral displacement estimation using tissue incompressibility. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control.* 1996; 43:247–56.
25. Chen X, Zohdy MJ, Emelianov SY, O'Donnell M. Lateral speckle tracking using synthetic lateral phase. *IEEE Transactions on Ultrasonics Ferroelectrics & Frequency Control.* 2004; 51:540–50.
26. Ebbini ES. Phase-coupled two-dimensional speckle tracking algorithm. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2006; 53:972–90. [PubMed: 16764451]
27. Brusseau E, Kybic J, Deprez JF, Basset O. 2-D locally regularized tissue strain estimation from radio-frequency ultrasound images: theoretical developments and results on experimental data. *IEEE Trans Med Imaging.* 2008; 27:145–60. [PubMed: 18334437]

28. Konofagou E, Ophir J. A new elastographic method for estimation and imaging of lateral displacements, lateral strains, corrected axial strains and Poisson's ratios in tissues. *Ultrasound Med Biol*. 1998; 24:1183–99. [PubMed: 9833588]
29. Viola F, Walker WF. A spline-based algorithm for continuous time-delay estimation using sampled data. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2005; 52:80–93. [PubMed: 15742564]
30. Viola F, Coe RL, Owen K, Guenther DA, Walker WF. MUlti-Dimensional Spline-Based Estimator (MUSE) for motion estimation: algorithm development and initial results. *Ann Biomed Eng*. 2008; 36:1942–60. [PubMed: 18807190]
31. Jiang J, Hall T. A Generalized Speckle Tracking Algorithm for Ultrasonic Strain Imaging Using Dynamic Programming. *Ultrasound in Medicine & Biology*. 2009; 35:1863–79. [PubMed: 19682789]
32. Meunier J, Bertrand M. Ultrasonic texture motion analysis: theory and simulation. *IEEE Transactions on Medical Imaging*. 1995; 14:293–300. [PubMed: 18215833]
33. Pavan TZ, Madsen EL, Frank GR, Jiang J, Carneiro AA, Hall TJ. A nonlinear elasticity phantom containing spherical inclusions. *Phys Med Biol*. 2012; 57:4787–804. [PubMed: 22772074]
34. Fung, YC. *Biomechanics : mechanical properties of living tissues*. 2nd ed.. Springer-Verlag; New York: 1993. p. xviii. 568
35. Gelfand, IM.; Fomin, SV.; Silverman, RA. *Calculus of variations*. Dover Publications; Mineola, N.Y.: 2000. p. vii. 232
36. Zhu Y, Hall TJ. A modified block matching method for real-time freehand strain imaging. *Ultrasonic imaging*. 2002; 24:161–76. [PubMed: 12503771]
37. Vogel, CR. *Computational methods for inverse problems*. Society for Industrial and Applied Mathematics; Philadelphia: 2002. p. xv. 183
38. Chartrand, R. *Numerical differentiation of noisy, nonsmooth data*. Los Alamos National Laboratory; Los Alamos, NM 87544, United States: 2007.
39. Nock, LF.; Brunke, SS.; Jiang, H.; Mai, JJ.; Trahey, GE.; Von Behren, P. 2002 IEEE Ultrasonics Symposium, Oct 8-11 2002. Institute of Electrical and Electronics Engineers Inc.; Munich, Germany: 2002. A new medical ultrasound research interface.; p. 1571-3.
40. Song X, Pogue BW, Jiang S, et al. Automated region detection based on the contrast-to-noise ratio in near-infrared tomography. *Appl Opt*. 2004; 43:1053–62. [PubMed: 15008484]
41. Walker WF, Trahey GE. Fundamental limit on delay estimation using partially correlated speckle signals. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*. 1995; 42:301–8.
42. Thitaikumar A, Mobbs LM, Kraemer-Chant CM, Garra BS, Ophir J. Breast tumor classification using axial shear strain elastography: a feasibility study. *Phys Med Biol*. 2008; 53:4809–23. [PubMed: 18701768]
43. Barbone PE, Bamber JC. Quantitative elasticity imaging: what can and cannot be inferred from strain images. *Physics in Medicine & Biology*. 2002; 47:2147–64. [PubMed: 12118606]
44. Oberai AA, Gokhale NH, Goenezen S, et al. Linear and nonlinear elasticity imaging of soft tissue in vivo: demonstration of feasibility. *Phys Med Biol*. 2009; 54:1191–207. [PubMed: 19182325]
45. Arfken, GB. *Mathematical methods for physicists*. 3rd ed.. Academic Press; Orlando: 1985. p. xxi. 985

Figure 1.

A flowchart illustrating the procedures of the proposed PDE-based de-noising algorithm

Fig. 2.

Comparisons of error variances for (a) axial and (b) lateral displacements at different axial compressions (0.1% - 5%). The solid curves represent results from the QBM algorithm, while the dashed curves denote the results from the proposed PDE-based denoising algorithm.

Fig. 3.

Resultant Images of Case P obtained from QBM³¹ and the proposed algorithm: a) A B-mode image indicating a spherical target in a TM gelatin phantom. (b) and (c) are axial displacement images, while (c) and (d) are lateral displacement images. (f) and (g) are axial strain images. (h) and (i) are lateral strain images. Images in the middle and right columns are results from QBM and the proposed method, respectively. The arrows on (a) and (i) point to the spherical target and. Arrows on (e) indicate some (horizontal) striking artifacts induced by the proposed method. The contour on (g) is the segmented target boundary and was used for calculations of CNRs. The unit for displacements is millimeter

Fig. 4. Resultant Images of Case B obtained from QBM³¹ and the proposed algorithm, respectively: a) A B-mode image indicating a spherical target in an in vivo breast Fibroadenoma. (b) and (c) are axial displacement images, while (c) and (d) are lateral displacement images. (f) and (g) are axial strain images. (h) and (i) are lateral strain images. Images in the middle and right columns are results from QBM and the proposed method, respectively. The arrows on (a) point to the spherical target and. Arrows on (b) and (d) indicate tracking errors from the QBM algorithm The contour on (g) is the segmented target boundary and was used for calculations of CNRs. Arrows on (e) and (i) depict the “slipping” boundaries around the benign breast lesion. The unit for displacements is millimeter

Fig. 5.

Resultant Images of Case M obtained from QBM³¹ and the proposed algorithm, respectively: a) A B-mode image indicating a spherical target in an in vivo breast invasive ductal Carcinoma. (b) and (c) are axial displacement images, while (c) and (d) are lateral displacement images. (f) and (g) are axial strain images. (h) and (i) are lateral strain images. Images in the middle and right columns are results from QBM and the proposed method, respectively. The arrows on (a) point to the spherical target, while arrows on (b), (d) and (f) indicate tracking errors from the QBM algorithm. The contour on (g) is the segmented target boundary and was used for calculations of CNRs. The unit for displacements is millimeter.

Table 1

Performance of the proposed PDE-based algorithm for a numerical phantom, as compared to the QBM algorithm. Reduction factor is defined as the ratio between QBM and PDE. If the reduction factor is greater than 1 the PDE-based algorithm has a net effect for noise removal.

Level of Compression	Reduction Factor	
	Axial	Lateral
0.1%	4.15	13.33
0.5%	2.94	17.78
1%	1.45	14.40
2%	0.48	7.08
3%	0.23	4.48
4%	0.13	2.70
5%	0.09	1.93

Table 2

Summary of performance indices reflecting the outcome by the proposed algorithm. Three metrics: motion compensation accuracy and CNRs for axial (CNR_a) and lateral (CNR_l) strains. “Before” and “After” in the table below stands for the original (QBM) and processed data by the PDE algorithm, respectively.

Case #	Motion Tracking Accuracy (ρ_f)		CNR_a		CNR_l	
	Before	After	Before	After	Before	After
P (Fig. 3)	0.96	0.96	3.76	3.78	0.33	0.57
B (Fig. 4)	0.88	0.82	1.00	1.37	0.03	0.24
M (Fig. 5)	0.75	0.70	1.68	1.82	0.31	1.21