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Improving the Robustness of Time-of-Flight Based Shear Wave Speed Reconstruction Methods Using RANSAC in Human Liver *in vivo*

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Abstract

The stiffness of tissue can be quantified by measuring the shear wave speed (SWS) within the medium. Ultrasound is a real-time imaging modality capable of tracking the propagation of shear waves in soft tissue. Time-of-flight (TOF) methods have previously been shown to be effective for quantifying SWS from ultrasonically tracked displacements. However, the application of these methods to *in vivo* data is challenging due to the presence of additional sources of error, such as physiological motion, or spatial inhomogeneities in tissue. This paper introduces the use of random sample consensus (RANSAC), a model fitting paradigm robust to the presence of gross outlier data, for estimating the SWS from ultrasonically tracked tissue displacements *in vivo*. SWS reconstruction is posed as a parameter estimation problem, and the RANSAC solution to this problem is described. Simulations using synthetic TOF data show that RANSAC is capable of good stiffness reconstruction accuracy (mean error 0.5 kPa) and precision (standard deviation 0.6 kPa) over a range of shear stiffness (0.6 – 10 kPa) and proportion of inlier data (50 – 95%). As with all TOF SWS estimation methods, the accuracy and precision of the RANSAC reconstructed shear modulus decreases with increasing tissue stiffness. The RANSAC SWS estimator was applied to radiation force induced shear wave data from 123 human patient livers acquired with a modified SONOLINE Antares ultrasound system (Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA, USA) in a clinical setting before liver biopsy was performed. Stiffness measurements were not possible in 19 patients due to the absence of shear wave propagation inside the liver. The mean liver stiffness for the remaining 104 patients ranged from 1.3 – 24.2 kPa, and the proportion of inliers for the successful reconstructions ranged between 42 – 99%. Using RANSAC for SWS estimation improved the diagnostic accuracy of liver stiffness for delineating fibrosis stage when compared to ordinary least squares (OLS) without outlier removal (AUROC = 0.94 for $F \geq 3$ and AUROC = 0.98 for $F = 4$). These results show that RANSAC is a suitable method for estimating the SWS from noisy *in vivo* shear wave displacements tracked by ultrasound.

Keywords

acoustic radiation force; hepatic fibrosis; shear wave; stiffness; ultrasound

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Introduction

Tissue stiffness is often related to underlying pathology. For example, palpation alone is effective in detecting a variety of illnesses, including lesions, aneurysms, and inflammation. In some ailments, such as liver fibrosis, disease progression may be marked by a gradual change in tissue stiffness, leading to a spectrum of changes in material properties. The ability to non-invasively quantify tissue stiffness *in vivo* may be useful in the staging and management of such diseases.

Recently, a number of imaging methods have been developed for quantifying tissue stiffness *in vivo* using shear waves. These systems generate shear waves in tissue using either external mechanical excitation coupled to the body wall, (Yin et al, 2007; Huwart et al, 2006; Sandrin et al, 2003), or acoustic radiation force to remotely palpate tissue at the focal region of the acoustic beam (Sarvazyan et al, 1998; Bercoff et al, 2004; Chen et al, 2004; Palmeri et al, 2008). The propagation of these shear waves are monitored in space and time by a real-time imaging modality such as magnetic resonance imaging (MRI) or ultrasound. The speed of shear wave propagation can then be related to the underlying tissue stiffness.

A fundamental challenge in quantifying tissue stiffness using shear waves is the estimation of shear wave speed (SWS) from dynamic displacement data. One method is algebraic inversion of the Helmholtz equation, which requires computation of second-order derivatives. This has been successfully applied to MRI data (Sinkus et al, 2005; Oliphant et al, 2001), but with limited success to ultrasound (Bercoff et al, 2004; Sandrin et al, 2002; Nightingale et al, 2003), due to the noisy nature of ultrasound displacement estimates. Another technique involves estimation of either the spatial or temporal frequency of the shear wave, given *a priori* knowledge of its counterpart (Yin et al, 2007; Chen et al, 2004; McAleavey et al, 2007). However, these methods require generation of monochromatic shear waves of known spatial or temporal frequency. An alternative method of SWS estimation is the so-called time-of-flight (TOF) approach. The shear wave arrival time is determined at multiple spatial locations. By assuming a fixed direction of propagation, the SWS can then be calculated using linear regression. This method has been successfully used on ultrasound tracked shear wave displacement data by multiple groups (Sandrin et al, 2003; McLaughlin and Renzi, 2006; Tanter et al, 2008; Palmeri et al, 2008).

While TOF SWS estimation has been validated on simulation and phantom data (Palmeri et al, 2008), its use in *in vivo* patient data presents additional challenges. Physiological motion, low displacement signal-to-noise ratio (SNR) and spatial inhomogeneities in tissue can corrupt estimates of shear wave arrival times. Approaches currently used by TOF algorithms to deal with noisy data include smoothing by averaging SWS reconstructions over multiple locations, employing goodness-of-fit criteria to remove unreliable linear regression results, and iteratively removing data with the largest residual after least squares fitting. However, these methods are not robust in the presence of gross outliers, which, unlike measurement uncertainty, do not follow a normal distribution. Uncompensated gross outliers can have two deleterious effects:

1. skew linear regression results and SWS estimates
2. render 'good' data inadmissible by lowering goodness-of-fit metrics

Random sample consensus (RANSAC) is a widely used iterative fitting algorithm capable of interpreting data containing significant numbers of gross outliers (Fischler and Bolles, 1981). In this paper, the RANSAC fitting paradigm is applied to the problem of TOF SWS estimation from ultrasound tracked shear wave displacements induced by acoustic radiation force as described by Palmeri et al (2008). Implementation details of the RANSAC

algorithm for SWS estimation are described, and approaches for tuning various parameters of the algorithm are outlined. The performance of RANSAC SWS estimation is evaluated on simulated noisy data sets containing outliers, as well as experimentally acquired data from *in vivo* human liver.

Methods

Data Acquisition

Experimental shear wave data was acquired using a modified SONOLINE Antares ultrasound system (Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA, USA). Imaging parameters are summarized in Table 1. The acquisition sequence consists of three *reference* A-lines, followed by a high intensity *pushing* line to mechanically excite the tissue, then by 80 repeated *tracking* A-lines. The *reference* and *tracking* A-lines were located at the same spatial position and were used to monitor tissue motion before and after radiation force excitation, respectively. This ensemble was repeated nine times with the pushing location held fixed and the reference and tracking locations increasingly further away in order to track shear wave propagation away from the region of excitation. 4:1 parallel receive was implemented to reduce the number of interrogations required and shorten acquisition time to minimize the effect of patient motion (Dahl et al, 2007).

In vivo shear wave data was acquired in the liver of 123 patients before undergoing liver biopsy at Duke University Medical Center in an IRB approved study. All subjects were informed of the nature and aims of this study and signed a consent form. Imaging was performed during breath holds with the probe viewing the liver from an intercostal or subcostal location. The number of independent shear wave acquisitions performed on different breath holds in each patient ranged from six to twelve.

Data Processing

All data processing, including the RANSAC algorithm, was performed in the MATLAB (The MathWorks, Natick, MA) environment on a Linux cluster with an average CPU speed of 2.6 GHz. Tissue motion due to acoustic radiation force excitation was measured by Loupas' method on IQ data (Pinton et al, 2006). A threshold value of 0.95 for the magnitude of the complex correlation coefficient was used to remove reverberation echoes and poor displacement estimates. A quadratic motion filter was used for *in vivo* data to reduce the effect of physiological motion. This filter fits a quadratic function to the displacement at time-steps when the tissue is not perturbed by the shear wave in order to estimate underlying tissue motion. The time-steps used for fitting were the three pre-push *references*, and post-push tracks at times greater than 9 ms after the peak displacement, when motion due to the shear wave is assumed to be negligible. A low-pass filter with a cutoff frequency of 1 kHz was used to remove high frequency jitter from the temporal displacement profiles. The resulting shear wave displacement after filtering at the focal depth lateral to the excitation location obtained on one patient is shown in Figure 1(b).

Shear wave transit time was measured using the time-to-peak (TTP) approach described by Palmeri et al (2008). The peak displacement time of the shear wave at lateral locations away from the excitation region was determined as shown in Figure 1(b). Data within the excitation beamwidth laterally were not used to avoid diffraction effects within this region. The excitation beamwidth is approximated by $(F/\#)\lambda = 1.4$ mm, where $F/\# = 2$ is the excitation beam f-number, and $\lambda = 0.7$ mm the excitation wavelength. Shear wave TTP analysis was also restricted to an axial depth of field (DOF) defined by $8(F/\#)^2\lambda = 22$ mm centered around the focal depth of the excitation beam (Palmeri et al, 2008), where the direction of shear wave propagation is assumed to be parallel to the lateral dimension. The

2-dimensional (2D) region of interest (ROI) over which TTP values are analyzed for SWS reconstruction is shown in Figure 1(a).

RANSAC SWS Reconstruction

RANSAC is a model fitting algorithm robust to the presence of outlier data (points not consistent with the model) proposed by Fischler and Bolles (1981). It proceeds by repeatedly performing the following steps for some number of iterations k :

1. **Hypothesize:** Generate a trial solution by randomly selecting a subset of points (minimal sample set (MSS)) to fit the model
2. **Test:** Identify points which do not match the model within the expected measurement error t as outliers
3. **Update:** Keep the trial solution if it produces a better fit than previous iterations, as determined by a cost function

The optimal fit is obtained by performing least squares using the set of inliers associated with the best trial solution found. In contrast to conventional smoothing techniques, RANSAC defers the smoothing operation until the last step of the algorithm, when it is applied only to consistent data.

The input to the RANSAC SWS algorithm is the set of TTP values extracted over a 2D ROI over lateral and depth dimensions (the box in Figure 1(a)). The goal of the algorithm is to find the parameters of a model which best fits the variation of TTP values over this spatial domain. To reconstruct the SWS, the following assumptions are made: (i) homogeneity of the tissue within the ROI, (ii) the direction of shear wave propagation is parallel to the lateral dimension, and (iii) negligible dispersion occurs within the ROI. Therefore, the following linear model was fit to TTP data:

$$\mathbf{z} = \beta_1 \mathbf{x} + \beta_2 \mathbf{y} + \beta_3 \quad (1)$$

where $\mathbf{x}$, $\mathbf{y}$ and $\mathbf{z}$ are vectors of lateral, depth, and TTP values respectively, and $\boldsymbol{\beta} = [\beta_1 \ \beta_2 \ \beta_3]$ are unknown model parameters. This corresponds to fitting a plane to the TTP values over a 2D grid. The SWS is then the inverse slope of the plane in the x dimension, given by $SWS = 1/\beta_1$. The shear modulus G can be calculated using $G = 1/\beta_1^2$, assuming tissue to be a linear elastic isotropic solid with a mass density of 1000 kg/m^3 . The extra degree of freedom β_2 was included to account for offsets in the measured TTP values in depth, and is expected to be close to zero in practice.

The minimum number of points required to fit a plane is three. Therefore, a MSS of three points was randomly selected to solve Equation 1 for each RANSAC iteration. Models produced by iterations corresponding to physically realistic shear wave speeds for human liver ($0 < SWS < 5.8 \text{ ms}^{-1}$) were kept for evaluation. Measurement error was assumed to occur only in the TTP dimension, so the following equation was used to calculate the distance ϵ of a given point $[x \ y \ z]$ to a plane:

$$\epsilon = \beta_1 x + \beta_2 y + \beta_3 - z. \quad (2)$$

The cost function used to rank models found from each RANSAC iteration is the redescending M-estimator proposed by Torr and Zisserman (2000):

$$C = \sum_i \rho(\epsilon_i^2) \quad (3)$$

where $\rho()$ is

$$\rho(\epsilon^2) = \begin{cases} \epsilon^2 & \text{if } \epsilon^2 < t^2 \text{ inlier} \\ t^2 & \text{if } \epsilon^2 \geq t^2 \text{ outlier,} \end{cases} \quad (4)$$

and t is the noise threshold used to separate inliers from outliers. Thus, outliers are given a constant penalty of t^2 , while inliers are scored on how well they fit the model. In other words, RANSAC seeks to fit a model to minimize the number of outliers and sum of the square errors of the inliers. If no minimum in the cost function is found within the expected range of β_1 in human liver ($0 < 1/\beta_1 < 5.8 \text{ ms}^{-1}$) over the repeated iterations, the algorithm indicates an unsuccessful fit.

Ideally, every possible combination of points should be considered for the MSS, but this is computationally prohibitive for large data sets. Instead, the number of RANSAC iterations k can be chosen to ensure with some probability z that at least one randomly chosen MSS for initializing the model is outlier free (Fischler and Bolles, 1981). If the proportion of inliers in the data is w , then the probability of picking at least one outlier every iteration $(1 - z)$ is given by

$$(1 - z) = (1 - w^3)^k, \quad (5)$$

which means that

$$k = \frac{\log(1 - z)}{\log(1 - w^3)}. \quad (6)$$

If $z = 0.99$, the minimum number of iterations required are shown in Table 2. In practice, w is not known *a priori*, therefore a worst-case scenario was assumed, and the number of iterations was set to 5000. The only penalty for selecting a large k is computation time. Since this algorithm was used for offline processing of data, speed was not a critical issue.

The noise threshold t used to identify outliers was set to the 99th percentile of the TTP measurement error (equivalent to $t = 2.58\sigma$, where σ is the standard deviation of the TTP error, which is assumed to be normally distributed). The TTP error distribution was determined experimentally from the residual fitting error after a first pass of RANSAC on all the patient data. For this first pass, a TTP error of $\sigma = 0.37 \text{ ms}$ measured from shear wave data acquired on a homogeneous elastic phantom (CIRS, Norfolk, VA, USA), was used to set an initial value of $t = 0.95 \text{ ms}$. The residual TTP error for the patients after the first pass of RANSAC is shown in Figure 2(a) for a shear wave propagation distance of $x = 10 \text{ mm}$. The estimated standard deviation of the TTP error is shown in Figure 2(b) for a range of distances. As expected, the TTP error increased with propagation distance, due to the lower amplitude of shear wave displacements. Therefore, a variable noise threshold $t(x)$, which linearly increases with lateral distance x from the excitation, was used to process the patient liver data to obtain the final results.

Every patient shear wave acquisition was manually evaluated by viewing the raw displacement data through time to ensure that a shear wave was successfully coupled into the ROI. SWS estimates from acquisitions in which there was no observable shear wave were discarded. Typically, acquisitions with no apparent shear wave propagation are characterized by RANSAC SWS reconstructions with a low number of inliers. Therefore, receiver operating characteristic (ROC) curve analysis was performed to determine whether thresholding using the number of inliers could be used to automatically reject RANSAC SWS estimates from acquisitions in which the ROI is not sufficiently perturbed by the shear wave.

Simulation

Simulations were performed to characterize the performance of RANSAC SWS reconstruction over a range of stiffness and percentage of gross errors. TTP points were generated in a spatial domain the same size as the experimental ROI shown in Figure 1(a). The sampling interval within this ROI was 0.1 mm laterally, and 0.035 mm in depth, also equivalent to experimental data. Ideal TTP values were generated using Equation 1 with $\beta_2 = 0$ and $\beta_3 = 1.75$ ms, (these values correspond to fitted parameters for the phantom data described previously). β_1 was allowed to vary in order to simulate a range of tissue stiffness. Points were randomly classified as inliers or outliers. For inliers, normally distributed measurement noise with variable standard deviation with lateral position, as shown in Figure 2(b), was added to the ideal TTP values. Outliers were assumed to have a uniform distribution in the range $[0, 16.4]$ ms (total tracking time) and truncated between $[TTP - t(x), TTP + t(x)]$ to ensure an error greater than the noise threshold $t(x)$. The RANSAC SWS algorithm was applied to simulated TTP data for a range of shear moduli ($0 < \mu < 26$ kPa) and inliers (30 – 95%). For each combination of shear modulus and number of inliers, 100 synthetic TTP data sets were generated (with different values but the same noise distribution). The same noise threshold and cost function used for processing patient data was used for the simulations. The number of RANSAC iterations k were allowed to vary between 3 – 169 for each data set in order to show the effect of k on estimated SWS (this range of k corresponds to values given by Equation 6 for the range of inliers simulated). As a comparison, ordinary least squares (OLS) without outlier removal was also applied to the same data sets for plane fitting and SWS quantification. The accuracy (mean error) and precision (standard deviation) of the reconstructed shear modulus over each of the 100 trials were computed for both RANSAC and OLS.

Results

Simulation

The RANSAC reconstruction accuracy and precision over 100 trials for all the combinations of shear modulus and percentage of inliers simulated are shown in Figure 3. The number of RANSAC iterations used to obtain these results was 169 (the maximum simulated). Both the reconstruction accuracy and precision decrease as the shear modulus increases and the number of inliers decreases. The RANSAC reconstruction results are compared to OLS fitting for SWS estimation using the same data in Figure 4 over a truncated domain. It can be seen that the SWS reconstruction error using OLS without outlier removal increases significantly for only modest reductions in the number of inliers and increase in shear modulus. In contrast, the RANSAC reconstruction error remains low. The RANSAC precision was comparable to OLS.

The effect of varying the number of iterations on SWS reconstruction accuracy and precision is illustrated in Figure 5 for a simulated stiffness of 2.5 kPa. The data shown was obtained from 100 trials for each combination of percentage of inliers and RANSAC

iterations. As expected, both the RANSAC reconstruction accuracy and precision decreases with the number of iterations. In addition, the number of iterations required to achieve comparable accuracy and precision increases as the number of inliers decrease. The number of iterations required to satisfy Equation 6 for $z = 0.99$ (probability to ensure that at least one MSS is outlier free) is also shown in Figure 5. It can be seen that this relationship can be used as a guide for choosing the number of iterations required to maintain SWS reconstruction accuracy and precision, given the proportion of inliers in the data.

Patient Data

The average run-time for RANSAC to process one patient liver acquisition (5000 iterations, not including pre-processing of displacement data and extracting TTP values), was 186 seconds. Examples of RANSAC SWS reconstruction results for four livers are shown in Figure 6. The B-mode ultrasound within the ROI is displayed with locations of TTP inliers (blue) and outliers (red) classified by RANSAC overlaid on top. TTP values are unavailable at locations of low displacement amplitude. The right side of the ROI represent locations furthest from the excitation which may not be perturbed by the shear wave due to attenuation and geometric spreading.

In Figure 6(a), very few outliers were detected, indicative of a shear wave of constant velocity traveling over a homogeneous region of the liver inside the ROI. In Figure 6(b), a diagonal band of outliers at the bottom of the ROI were detected. The shear wave was unable to propagate beyond this band. This spatial distribution of outliers is consistent with the B-mode appearance of the liver at the same approximate location, which shows a diagonal band of hypoechogenicity. This suggests that a non-uniform structure within the ROI, such as a vessel, was present. In Figure 6(c), a vertical stripe of outliers was detected. The displacement data at these lateral locations were obtained using parallel receive from the same push (recall that 9 repeated reference-push-track ensembles were necessary to acquire data over the entire ROI). This suggests that excessive physiological motion occurred during this particular ensemble which corrupted the shear wave displacements, and was not able to be corrected by the quadratic motion filter. Nevertheless, RANSAC was able to remove these corrupted TTP values. In Figure 6(d), the number of TTP data points available are low and sparsely distributed within the ROI. This is characteristic of low displacement amplitudes and cases where the shear wave fails to propagate inside the ROI. Even though RANSAC was able to reconstruct a shear modulus in this case using a limited number of inliers, this acquisition was manually characterized as invalid with no observable shear wave.

In the 123 patient livers, a total of 1222 shear wave acquisitions were performed. Of these acquisitions, RANSAC was able to successfully reconstruct the shear modulus (within physical limits as previously described) in 787 cases. Of the 435 acquisitions for which RANSAC failed to return a physically realistic SWS, 400 had been independently ruled out by manual inspection as bad acquisitions where a shear wave failed to propagate in the ROI. Out of the 787 successful reconstructions, a subset of 605 were from acquisitions manually classified with observable shear wave propagation, and were considered to be valid measurements. The proportion of TTP data which were inliers for valid reconstructions ranged from 42 – 99%. The number of patients having at least one valid stiffness measurement was 104 (85%). The mean liver stiffness for these patients ranged from 1.3 – 24.2 kPa. The fibrosis scores for 92 of these patients were available from biopsy results. The distribution of mean liver stiffness for these 92 patients are shown in Figure 7 grouped by fibrosis stage.

The diagnostic accuracy of mean liver stiffness for predicting fibrosis stage was assessed using ROC curve analysis, shown in Figure 8. The optimum cutoff values for stiffness were

calculated to maximize the true positive rate and minimize the false positive rate, and are shown in Table 3, along with the areas under the ROC curve (AUROC). To compare the performance of RANSAC and OLS, the same shear wave acquisitions were reprocessed using OLS without outlier removal. The ROC curves using OLS are shown on the same axes as the corresponding RANSAC ROC curves in Figure 8. The OLS AUROC are also tabulated in Table 3 for comparison. It can be seen that RANSAC stiffness estimation resulted in better delineation of fibrosis stage compared to OLS for patients with severe fibrosis ($F \geq 3$ and $F=4$).

The optimal cutoff value for the inlier size as a threshold for delineating valid SWS measurements was 22000 points, as determined from ROC curve analysis. This gave a true positive rate of 84% and a false positive rate of 13%, compared to manual verification of shear wave propagation as a gold standard. Recall that manual verification resulted in 104 patients with at least one valid stiffness measurement. With automatic thresholding, the mean stiffness of 52 (50%) of these patients remained unchanged, while 6 (6%) patients were left without a single valid measurement. For the remaining 46 (44%) patients, the mean liver stiffness was different between automatic and manual validation. In 18 of these cases, the standard deviation of measurements validated by thresholding increased to greater than half its mean value. If these 18 patients and the 6 livers without a single valid measurement as validated by thresholding are discarded, the average difference (bias) between the mean liver stiffness from thresholding and manual validation is -0.084 kPa, and the standard deviation of the difference is 0.64 kPa.

The RANSAC reconstruction results presented so far have utilized a noise threshold $\sigma(x)$ which is variable over the ROI lateral range. As described previously, this noise threshold was determined by a first-pass of RANSAC over the patient liver data using an initial guess of a constant threshold estimated from phantom data. The differences between the RANSAC stiffness reconstruction results from using the constant threshold and the refined variable threshold was examined. The mean difference (bias) is -0.019 kPa and the 95% confidence interval for the difference is ± 0.91 kPa.

Discussion

The simulation results using synthetic TTP data show that RANSAC is able to maintain good reconstruction accuracy and precision over a range of tissue stiffnesses and numbers of gross outliers that may be encountered in *in vivo* radiation force induced shear wave data in human liver. As expected, both the accuracy and precision of the estimated shear modulus decreases as the number of outliers present in TTP data increases. However, this reduction is modest for soft media. For example, for tissue up to 10 kPa, which represents the majority of liver stiffness we have encountered so far, the mean reconstruction error was < 0.5 kPa, and the precision was < 0.6 kPa for an inlier proportion of only 50%. In stiffer media, the reduction in reconstruction accuracy and precision is more prominent. The reason for this is that the slope of the plane fitted by RANSAC (Equation 1) is related to the shear modulus by an inverse square relationship. This property is common for all TOF SWS estimation methods, and is not specific to RANSAC. For large values of shear modulus, small variations in the slope of the fitted plane translate into large errors in the reconstructed shear modulus. Therefore, both the accuracy and precision of shear modulus reconstructions decrease as the tissue stiffness increases.

An additional factor specific to RANSAC which can result in a decrease in reconstruction accuracy and precision is that it is a non-deterministic algorithm. That is, repeated executions of RANSAC on the same data set can yield varying values of shear modulus, provided a finite number of iterations are used. This is due to the random selection of the

MSS at each iteration. Unless all possible combinations of points are selected within the number of iterations available, RANSAC does not probe all possible initial configurations for the model parameters. Thus, the optimization for the best fit plane is performed over different subsets of parameter space for each execution of the algorithm. For data sets containing a large percentage of inliers, the parameter space spanned by all possible MSS is small. Therefore, repeated RANSAC reconstructions are likely to lead to the same shear modulus, even if only a small subset of all possible MSS is sampled. For data sets containing a small proportion of inliers, the parameter space spanned by all possible MSS is enlarged due to the random distribution of outliers. This reduces the probability that repeated operations of RANSAC will sample the same model parameters and arrive at the same solution for the best fit plane, hence decreasing accuracy and precision. The effect of varying the number of RANSAC iterations for a range of inlier percentages is shown in Figure 5 for a simulated shear modulus of 2.5 kPa. It can be seen that Equation 6 may be used to predict the number of iterations in order to maintain reconstruction accuracy and precision, given an estimate for the proportion of inliers in the data. In the current study, a worst case scenario was assumed, and 5000 iterations was used to mitigate the effects of undersampling the parameter space in data sets containing large numbers of outliers.

The results obtained with patient liver data demonstrate that RANSAC SWS reconstruction can be successfully applied to *in vivo* shear wave data. As shown by the ROC curves in Figure 8, RANSAC outperformed OLS in classifying patients with severe fibrosis ($F \geq 3$ and $F=4$). For moderate fibrosis ($F \geq 2$), both RANSAC and OLS had similar AUROC, likely due to the small differences in stiffness between F0-F2 livers. This trend of low stiffness in healthy to moderately fibrotic livers, and marked stiffness increase in severely fibrotic and cirrhotic livers, has also been observed in studies using magnetic resonance elastography (MRE) (Huwart et al, 2006; Yin et al, 2007) and the Fibroscan system (Friedrich-Rust et al, 2008) for measuring liver stiffness.

For the patient liver data, using the number of inliers as a threshold to automatically identify valid SWS measurements could achieve a true positive rate of 84% and a false positive rate of 13% compared to manual verification of valid SWS measurements as a gold standard. In combination with post-processing removal of patients with large standard deviations in stiffness, automatic thresholding did not introduce significant bias in the mean liver stiffness (mean difference = -0.084 kPa, standard deviation = 0.64 kPa). However, it reduced the number of patients with a valid stiffness measurement by 24 (23%). Therefore, manual validation of acceptable SWS measurements were used for analysis herein. The number of patients with successful stiffness measurements could be increased in future studies if real-time feedback indicating whether a shear wave was successfully coupled into the ROI was available. This could potentially allow automatic thresholding to be used, since repeat acquisitions in cases of invalid measurements can be performed.

The RANSAC algorithm can be readily applied for SWS estimation in other tissue types besides the liver. Consideration must be given, however, to the noise threshold, which should ideally be chosen to match the expected TTP measurement error. The magnitude of this error depends on a host of factors, including the excitation focal configuration, tracking jitter, and mechanical behavior of the tissue. It can be experimentally determined using the approach previously described in the Methods section. For the cost function used (Equation 3), as the noise threshold approaches infinity, the RANSAC solution becomes equivalent to OLS and subject to the influence of gross outliers. In contrast, a noise threshold which is too small will result in most points being identified as outliers, giving rise to a non-discriminating cost function for ranking trial solutions. For the patient livers, the result of using a constant noise threshold measured from phantom data was compared to that of a variable threshold, which more accurately models the inlier noise distribution. There was no

bias in the difference between the reconstructed shear modulus using the two noise thresholds on the same data (mean difference = -0.019 kPa, 95% confidence interval = ± 0.91 kPa). In applications where an error of this magnitude can be considered insignificant, using a 'ballpark' approximation for the noise threshold measured from a phantom may be sufficient.

A limitation of the RANSAC SWS reconstruction algorithm, which is common to all TOF based methods, is the assumption that tissue behaves as a linear elastic material. However, the liver is known to exhibit viscoelastic (VE) behavior (Huwart et al, 2006; Chen et al, 2009; Muller et al, 2009; Deffieux et al, 2009). In a VE material, the SWS is a function of frequency. Therefore, the broadband shear wave used to excite the liver in the present study will experience shifts in the relative phases of its constituent frequency components. As a result, the morphology of the shear wave will change as it propagates through the liver. The measured velocity of the peak displacement used herein effectively represents a 'bulk' velocity of the liver. This bulk velocity lies in-between the speeds of the fastest and slowest frequency components of the shear wave. In order to capture the full VE behavior of the liver, higher order characteristics of the shear wave, besides its time to peak displacement, would have to be analyzed.

Another limitation of the SWS reconstruction approach presented herein is its spatial resolution. Currently, tissue homogeneity is assumed, and one single SWS is calculated for the entire ROI. This approach is appropriate when one is interested in the overall mean stiffness of the tissue, and the assumption of homogeneity can be reasonably met. However, when the region inside the ROI is not homogeneous, an image depicting the spatial variation of tissue stiffness may be more useful. One potential method of achieving a finer spatial resolution would be to divide the ROI into multiple sub-regions, and independently process the data within these with RANSAC. The trade-off would be to maintain an adequate level of SWS reconstruction accuracy with the limited data available within these sub-regions.

The MI value of the pushing pulse used herein was 3.2. While this is higher than the limit of 1.9 imposed for clinical applications, we believe the acoustic energy used to interrogate the patient livers in this study to be safe, and the risk of cavitation extremely unlikely, given the lack of cavitation nuclei (i.e. air, or gaseous bubbles such as contrast agents) inside the liver. The *in situ* peak negative pressure is also likely to be lower due to the higher attenuation coefficient of the liver and intervening fat tissue than the standard derating factor of 0.3 dB/cm MHz used to calculate the MI. To meet requirements for clinical use, parameters of the pushing pulse, including frequency, duration, and intensity, would be further optimized.

The average run-time of the RANSAC algorithm as it is currently implemented for the patient liver data is 186 seconds, which is unsuitable for real-time SWS estimation. However, neither the software environment nor the code have been optimized for speed in the current study. Therefore, significant improvements in the run-time of the algorithm may be possible and could facilitate its use for real-time processing. In addition, the algorithm itself could be modified to improve speed. For example, the largest number of putative inliers found in the data could be checked after every iteration. This number could be used to terminate the algorithm once it is higher than some threshold, or be used to update the number of iterations required according to Equation 6. The computational burden of RANSAC could also be reduced by performing spatial averaging of displacement or TTP data to reduce the number of data points.

Conclusion

This paper has demonstrated the application of the RANSAC fitting paradigm to the problem of robust SWS estimation from ultrasonically tracked shear wave displacements. In contrast to other methods of SWS estimation from TOF data, RANSAC is able to interpret data containing significant numbers of gross outliers. In synthetic simulated TTP data, RANSAC was able to maintain good reconstruction accuracy (mean error < 0.5 kPa) and precision (standard deviation < 0.6 kPa) over a range of stiffness (0.5 – 10 kPa), and proportion of inliers (50 – 95%). Like all TOF SWS estimators, the accuracy and precision decreases with increasing stiffness due to the inverse square relationship between the parameters optimized by RANSAC and the shear modulus. In *in vivo* patient liver data, RANSAC successfully reconstructed the shear modulus in 104 out of 123 patients (85%). Almost all unsuccessful reconstructions were associated with the absence of a propagating shear wave inside the ROI, which was independently verified by visual inspection of displacement data through time. The mean liver shear modulus for the successful reconstructions ranged from 1.3 – 24.2 kPa, and the proportion of inliers ranged between 42 – 99%. Compared to OLS, liver stiffness reconstructed with RANSAC resulted in better diagnostic accuracy of patients with severe fibrosis (AUROC = 0.94 for $F \geq 3$ and AUROC = 0.98 for $F = 4$). These results show that RANSAC is a suitable method for SWS estimation from *in vivo* ultrasonically tracked shear wave displacements. The spatial resolution of the RANSAC SWS estimator, as it is currently implemented, can be improved. With optimizations for speed, it may also be possible to use RANSAC for real-time SWS estimation.

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Figure 1.

(a) *In vivo* B-mode image of a patient liver, outlined with the ROI over which TTP data is extracted. The excitation occurs at a lateral location of 0 mm and is focused at 49 mm. (b) The measured tissue axial displacement after filtering at the excitation focal depth due to radiation force excitation. Each curve shows the tissue displacement as a function of time after the excitation. The lateral location of each curve with respect to the excitation location are shown in the legend. The vertical dotted lines show the measured TTP values used for shear wave speed estimation.

Figure 2.

(a) TTP fit error distribution from all patient shear wave measurements for a shear wave propagation distance of 10 mm and estimated standard deviation. (b) The estimated standard deviation of the TTP error from patients for different shear wave propagation distances, and the least squares trend line used for setting the linearly varying noise threshold used for RANSAC SWS estimation.

Figure 3. RANSAC reconstruction accuracy and precision over 100 simulated TTP data sets for different combinations of shear modulus and percentage of inliers.

Figure 4. Comparison of RANSAC and OLS SWS reconstruction accuracy and precision for the same simulated TTP data sets for a range of shear modulus and percentage of inliers over 100 trials.

Figure 5. RANSAC reconstruction accuracy and precision for a simulated stiffness of 2.5 kPa and a range of inliers and iterations over 100 trials. The number of iterations required to satisfy Equation 6 with a probability $z = 0.99$ is shown as the white curve.

Figure 6.

B-mode images of four patient livers within the ROI overlaid with locations of available TTP data from one shear wave acquisition. TTP data classified by RANSAC as inliers are shown in blue and outliers are shown in red. The excitation occurs at a lateral location of 0 mm and is focused at 49 mm. The shear wave propagates from left to right in the ROI. In (a), few outliers are present, indicative of a shear wave traveling at constant velocity over a homogeneous medium. In (b), a band of outliers is present at approximately the same spatial location as a hypoechoic region in the B-mode, which suggests the presence of a structure, such as a vessel, in the ROI. In (c), a vertical stripe of outliers due to excessive patient motion was removed. In (d), few TTP points are available, indicative of an acquisition in which the shear wave failed to propagate in the ROI.

Figure 7. RANSAC shear modulus reconstruction results for the livers of patients grouped by fibrosis stage determined from liver biopsy. Each point represents the mean shear modulus obtained from multiple SWS measurements in each liver, while the error bars represent the standard deviation.

Figure 8.

ROC curves for detecting various stages of fibrosis using mean liver stiffness. The results for both RANSAC and OLS estimated stiffness are shown on the same axes. The optimal cutoff which maximizes sensitivity and specificity are shown for RANSAC.

Table 1

Summary of radiation force sequence parameters

Parameter	Value
Probe	CH4-1
Push freq	2.22 MHz
Track freq	3.08 MHz
Push cycles	400
Push duration	180 μ s
Track PRF	4.8 kHz
Push F#	2.0
Push focal depth (lateral)	49 mm
Elevation focus	49 mm
Peak temperature rise ΔT	0.2°C
I_{sppa} (<i>in situ</i>)	1662 W/cm ²
MI (0.3)	3.22
MI (<i>in situ</i>)	2.51

Minimum number of RANSAC iterations k required for fitting a plane to data with proportion of inliers w to ensure with probability 0.99 that at least one randomly selected MSS is outlier free

Table 2

w	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1
k	4	7	11	19	35	70	169	574	4603

Table 3

Optimal RANSAC stiffness cutoff for differentiating various fibrosis stages and AUROC. The AUROC for OLS is shown for comparison

	F≥ 2	F≥ 3	F= 4
Optimal Cutoff (kPa)	3.5	4.2	8.5
RANSAC AUROC	0.77	0.94	0.98
OLS AUROC	0.75	0.81	0.94