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VALIDATION OF SMURF ESTIMATION OF SHEAR MODULUS IN HYDROGELS

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Abstract

A validation study of the Spatially Modulated Ultrasound Radiation Force (SMURF) method for shear modulus estimation is presented. SMURF estimates of uniform gelatin and Zerdine™ phantoms covering a modulus range of 2 to 18 kPa are compared with results obtained by unconfined mechanical compression and sonoelastography. The results show agreement within the measurement uncertainties over the range indicated for all three methods. Repeatability and variation on the order of 5% of the phantom modulus are found for observations made at a single point within the phantom. Averaging of modulus estimates from several adjacent scan lines further decreases the variation. By using multiple radiation force peaks to induce a shear wave of known wavelength and measure the frequency of the wave, SMURF obtains modulus estimates from tracking data acquired along a single A-line. This is significant, as speckle can bias the measured phase of the shear wave. SMURF is shown to be insensitive to a constant phase error in the shear wave measurement. This results in greatly reduced correlated noise in the modulus estimates, in contrast with methods which track at multiple locations and do not cancel phase errors.

1. Introduction

Spatially Modulated Ultrasound Radiation Force (SMURF) is a method for shear modulus estimation using ultrasound tracking of shear waves induced by acoustic radiation force [1]. In this method an acoustic radiation force impulse with multiple, well-defined spatial intensity peaks is used to generate a shear wave of a designed wavelength. The frequency of this wave, tracked along a single A-line, is then used to estimate the shear modulus of the tissue. Non-invasive estimation of tissue shear modulus estimation is thought to have significant potential as a diagnostic test [2].

Acoustic radiation force based methods for examination of mechanical properties of tissue are currently under investigation by several groups. Radiation force methods were first proposed by Sarvazyan [3], who noted that the radiation force of a sufficiently intense ultrasound beam could be used to displace tissue distal to the transducer. The first trials of this method, acoustic radiation force impulse (ARFI) imaging, on a clinical scanner were by Nightingale et al. [4]. Ultrasound speckle tracking [5,6] or windowed cross-correlation tracking [7] is used to measure displacements induced by the beam and track its progress. A major advantage of acoustic radiation force based methods is that the tissue displacement is generated at the location of interest. Therefore, in contrast to surface driven methods (e.g. sonoelastography [8] and transient elastography [9]) the shear wave attenuation of tissue layers between the region of interest and the transducer does not interfere with shear wave generation. Furthermore, a simplification in apparatus is achieved because the same ultrasound transducer that generates tissue displacement can also be used to track it. The principle disadvantage of radiation force methods is the potential for tissue heating associated with the high ultrasound intensity needed to achieve measurable displacement [10,11,12]. The displacements induced are small, on the order of microns [4]. These small displacements are readily tracked, however,

because the signal-to-noise ratio (SNR) and correlation of echoes is very high; out of plane motion due to the radiation force displacement is negligible. A sub-micron displacement tracking noise floor typically is achieved in vivo [13,14]. Images of HIFU and RF induced lesions have been generated in phantoms [15] and in vivo [16], and our group has used this method to image excised human prostates [17]. Vibroacoustography [18] is another radiation force method, using two intersecting beams of slightly different frequency to produce a time-varying radiation force at the point of intersection. The time varying force has been used to examine breast tissue [19] and characterize tissue stiffness changes with therapy [20].

Quantification of shear modulus and other properties using acoustic radiation force is a more recent development. Viola et al. used repeated bursts of ultrasound to displace the vitreous and determine both modulus and an estimate of tissue viscosity using a Voight model of tissue [21]. Palmeri et al. described a method for estimating shear modulus by using the time to peak displacement at several locations in the path of an acoustic radiation force induced shear wave [22]. A linear fit to the arrival time estimates is used to reduce the variance of the shear wave velocity estimate, which is converted to modulus using the relationship $G = \rho c^2$. Supersonic Shearwave Imaging (SSI), described by Bercoff, Tanter, and Fink, estimates tissue viscoelastic properties by tracking the progress of radiation force induced shear waves with an ultrafast scanner [23]. Multiple ultrasound tone bursts focused at a sequence of depths and transmitted in rapid succession are used to create a pair of large amplitude shear waves. The propagating shear waves are distorted by variations in shear modulus. Inversion algorithms applied to the tracked motion data are used to recover the shear modulus. A method by Chen, Fatemi and Greenleaf called Shearwave Dispersion Ultrasonic Velocity measurement (SDUV) [24] estimates the phase shift as a function of distance from the point of excitation and beam difference frequency to estimate the elastic and viscous modulus of tissue. In contrast to SMURF imaging, where the tissue is excited with a known wavelength and tissue vibration frequency is estimated, in SDUV a known vibration is applied and wavelength is estimated.

Among these methods, SMURF is unique using a deliberate and carefully controlled spatial variation of radiation force to create a known shear wavelength, requiring tracking at only a single A-line to produce a modulus estimate. This is made possible by the use of the spatially modulated push beam that induces a shear wave with known spatial frequency or wavelength, equal to the lateral spatial frequency of the push beam. Using phased array beamforming, it is possible to create shear waves of a variety of wavelengths over a selected region within the field of view to interrogate shear modulus at a particular location. A particular advantage of this method, as will be shown, is the suppression of correlated jitter noise in the shear wave period estimate, and thus in the modulus estimate.

The goal of this paper is to validate the SMURF method for shear modulus estimation over a clinically relevant range of elastic moduli. This is accomplished through comparison of modulus estimates obtained in two types of uniform phantoms. Modulus estimates of the phantoms are generated using SMURF, unconfined compression, and tracking of externally, mechanically generated shear waves (sonoelastography).

2. Theory

We have introduced the SMURF method for shear modulus estimation previously [1,25]. The principle is to use acoustic radiation force to generate a shear wave of known *spatial* frequency k and measure the temporal frequency f of the material vibration as the wave propagates past a point. In a linear elastic material of density ρ the shear modulus G is related to the wavelength $\lambda = 2\pi/k$ and frequency of a harmonic wave by

$$G = \rho(\lambda f)^2. \quad (1)$$

Thus, by inducing a shear wave of known wavelength and measuring the resulting vibration frequency, tissue shear modulus may be estimated. Because it is the frequency of the radiation-force induced shear wave that is measured, instead of the wavelength, measurement of tissue motion is only required at a single point. There is no need for parallel receive beamforming to acquire the necessary data. SMURF replaces the challenging task of estimating shear wavelength with the simpler measurement of vibration frequency.

In a uniform, ultrasonically attenuating material with absorption coefficient α , plane or weakly focused ultrasound waves of intensity I gives rise to acoustic radiation force $F = 2\alpha I/c$, where c is the ultrasound wave speed [26]. The radiation force is a body force that acts throughout the propagating medium. The proportionality of radiation force to ultrasound intensity reduces creation of a spatially varying forcing function to a problem of creating an ultrasound beam with the desired spatial variation.

Several methods may be used to generate a specific spatially varying ultrasound beam intensity [27,28]. Our previous studies [1,25] used the constructive and destructive interference of two unfocused beams to generate the desired beam pattern. For instance, it is well known that the lateral pressure variation in the focal zone of a focused transducer is the Fourier transform of the apodization. This relationship allows the needed apodization for a particular intensity distribution to be calculated straightforwardly. More generally, intersecting ultrasound beams of identical frequency can produce a lateral pressure variation with no time dependence.

In this work a “sequential” push beam strategy is used, wherein the spatially varying radiation force is applied via a series of discrete, geometrically focused beams. This is feasible because of the 1000x difference between ultrasound and shear wave velocities and the relatively short duration of the pushing pulses (30 μ s) compared to the period of the shear waves (0.5–2 ms). The focal point of each beam in the push-beam sequence is translated by λ_s , the desired shear wavelength, relative to the previous push beam to generate the spatial variation in intensity and set the shear wavelength. The high transmit pulse repetition frequency (on the order of 10 kHz) compared to the expected shear wave frequency (200 Hz–2 kHz) allow the entire push beam sequence to be transmitted on a time scale that is short (though not insignificant) compared to the time scale of the shear wave dynamics.

3. Methods

3.1. Phantoms

3.1.1. Gelatin—Two phantoms were fabricated from 300 Bloom gelatin with a concentration of 30 g/liter and 61 g/liter DI water [29]. Powdered cornstarch was added to the gelatin mixture at a concentration of 160 g/liter to provide ultrasound scattering and attenuation.

Glutaraldehyde was added just before the gelatin mixture was poured into molds to increase phantom stiffness. The phantoms, roughly cylindrical with a mean radius and height of 7 cm, were rotated while setting to prevent settling of the mixture. After being allowed 24 hours to solidify, the phantoms were removed from the mold and stored under mineral oil when not in use.

3.1.2. Zerdine™—Four samples of Zerdine, a commercial ultrasonically tissue-mimicking phantom material, were obtained (CIRS, Inc., Norfolk, VA). The samples were cylindrical, with a diameter of 5.1 cm and height of 2.4 cm. The nominal ultrasound attenuation of all samples was of 0.5 dB/cm/MHz, and the ultrasound sound speed was 1540m/s. Individual

samples were homogeneous, both in acoustic properties and shear modulus. The samples spanned a shear modulus range of ~ 27 to ~ 18 kPa. The samples were obtained housed in PVC rings of 5.1cm inner diameter sealed on the flat ends with an acoustically transparent membrane to prevent desiccation. SMURF measurements were performed with the samples sealed within their housing, and removed only immediately prior to unconfined compression testing.

3.2. SMURF

A Siemens Antares scanner (Siemens Medical Solutions USA, Ultrasound Group) was used for pulse generation and echo acquisition. The scanner is equipped with the Ultrasound Research Interface [30] package, which allows acquisition of beamformed RF echo data sampled at 40 MHz and digitized with 16-bit resolution. Additional software allows modified transmit and receive beamforming sequences to be implemented on the scanner. SMURF estimates of modulus were performed using a Siemens VF10–5 linear array. This array contains 192 elements of 0.2mm pitch and 5 mm height. Elevation focusing is provided by a fixed lens, with a focus of approximately 2cm.

The beam sequence used for SMURF estimation of modulus in these studies is illustrated schematically in figure 1. The sequence consisted of thirty-two ensembles. Each ensemble begins with two pre-push reference “tracking” pulses, followed by a three-pulse “push” sequence, and finally 64 “tracking” pulses. The center frequency of both the push and track pulses was 6.67 MHz, and the period between start of pulses $79 \mu\text{s}$. The tracking beams spanned a lateral width of 4.6 mm, with a density of 6.67 lines/mm.

By keeping the location of the push beam group fixed and translating the track beam location between each successive ensemble, a sequence is developed that allows the propagation of the spatially modulated shear wave to be visualized. It should be noted, however, that while this particular sequence was designed to allow inspection of shear wave propagation in addition to modulus estimation, tracking at all locations is not necessary for SMURF. Estimates of modulus, as presented in the Results section, are generated from echoes from a single tracking location. A single ensemble as described here is sufficient for modulus estimation.

The tracking pulses, both before and after the push sequence, were standard 2-cycle-long B-mode pulses with a center frequency of 6.67 MHz. An apodized aperture, geometrically focused at a depth of 1.5 or 2 cm, was used for pulse transmission, while dynamic focusing and apodization were used on receive. Each of the three “push” pulses in an ensemble was 200 cycles long, geometrically focused at the same depth as the tracking pulses. The lateral spacing between foci was selected as either 1.5 or 1.95 mm. The F-number for each push beam was $F/3.3$ or $F/4.3$, respectively, with uniform weighting of transducer elements (i.e. no apodization). These F-numbers were selected such that the first lateral intensity nulls of one push beam would align with the those of its neighbor, as illustrated in figure 2.

Simulations of sequentially generated push beams are illustrated in figure 2. In these figures brightness is proportional to the ultrasound intensity integrated over the of the entire push beam sequence. Each of the three individual push beams was formed by a rectangularly-apodized, geometrically focused subaperture stepped across the transducer by the desired lateral modulation period. This approach faces a trade-off between lateral modulation frequency and the depth of field of the pushing region. The beam width at the focus is proportional to F-number of the subaperture. Narrower beams, and thus lower $F/\#$ s, are needed to maintain a clear distinction between the peaks and troughs of the lateral intensity profile as the lateral modulation frequency is increased. However, the depth of focus of an individual subaperture's beam is proportional to the F-number squared. The beams spacings selected represent a trade-o between these two effects.

Displacement estimates were generated from the RF echo data using normalized cross correlation [4]. The RF echo data were upsampled to 320 MHz using a low-pass interpolation filter that preserves the values of the original samples. Windows corresponding to a depth range of 1.16 mm were extracted from the data, and normalized cross correlation performed over a $20\text{ }\mu\text{m}$ search region. The location of the peak of resulting normalized correlation function was determined with sub-sample precision using a parabolic fit to the peak correlation sample and its neighbors. The tracking was performed about every sample point in the original data set, i.e. every $19.3\text{ }\mu\text{m}$. Finally, the material velocity was estimated by the finite difference

$v_{\vec{x}}[n] = (d_{\vec{x}}[n] - d_{\vec{x}}[n-1])/T$, where $d_{\vec{x}}[n]$ is the displacement at location $\vec{x}$ at the n^{th} time step, and T the pulse repetition period ($79\text{ }\mu\text{s}$). Prior to estimation of the frequency of the velocity signal, a second order polynomial fit to the velocity data through time at each location $\vec{x}$ was calculated. The polynomial fit was subtracted from the velocity data to eliminate low-frequency motion artifacts.

The period of the velocity signal was determined using an autocorrelation technique, wherein the lag of the first peak of the autocorrelation of the velocity signal is used to estimate the period. The autocorrelation of the velocity signal $R_{v_{\vec{x}}}[m]$ was calculated as

$$R_{v_{\vec{x}}}[m] = \sum_n v_{\vec{x}}[n] v_{\vec{x}}[n+m]. \quad (2)$$

Zeros were used for values outside the sampled domain of v . The velocity signals were up-sampled by a factor of 10 along the “slow-time” (n) dimension prior to calculation of the autocorrelation, increasing the effective pulse repetition frequency to 127 kHz, to improve the resolution of the frequency estimate. The lag corresponding to the fundamental period of the vibration signal at location $\vec{x}$ was taken to be the lag corresponding to the peak of $R_{v_{\vec{x}}}[m]$ in the range $m_{\min} < m < \infty$, where $m_{\min}$ is the lag of the minimum $R_{v,v(z,m)}$ for a given z . The frequency f of the SMURF-induced shear wave is taken to be the reciprocal of the lag thus identified. A sample autocorrelation trace, along with the identified peak and $m_{\min}$ is shown in figure 3.

A measurement bias is introduced by the time delay between individual push beams making up a single sequential-push ensemble. The source of this bias is illustrated in figure 4. The first geometrically focused push beam is focused at location x at $t = 0$. The next beam in the push ensemble is focused at location $x + \lambda$ and transmitted T seconds later, and the third at $x + 2\lambda$. Each push pulse launches a wave crest in the positive and negative x directions, which propagates a distance $c_s T$ from the source before next push within the ensemble. For $-x$ -going shear waves this increases the distance between shear wave crests by $c_s T$, while for $+x$ -going waves the distance is decreased by the same amount. The effective shear wavelength is $\lambda_e = \lambda + \mp c_s T$, where the sign of the $c_s T$ term is positive for the $-x$ -going wave and vice versa.

Substituting λ_e into equation 1 and using the relationship $c_s = \sqrt{G/\rho}$ lets us write

$$G = \rho(\lambda \mp c_s T)^2 f^2 \quad (3)$$

$$\sqrt{\frac{G}{\rho}} = \lambda f \mp \sqrt{\frac{G}{\rho}} T f \quad (4)$$

$$\sqrt{\frac{G}{\rho}} (1 \pm fT) = f\lambda_s \quad (5)$$

$$G = \rho(\lambda f)^2 \frac{1}{(1 \pm fT)^2} \quad (6)$$

where the sign of fT is positive for $+x$ going wave and negative for the $-x$ going wave.

3.3. Sonoelastography

Sonoelastography measurements were performed using a Siemens VF7–3 linear array. Like the VF10–5, this array contains 192 elements of 0.2 mm pitch. The center frequency is 5.33 MHz. The element height is 7.5 mm, and the elevation focus is approximately at 3.8 cm.

As illustrated in figure 5, sequences for sonoelastography data acquisition consisted of B-mode type pulses fired at two positions, x_1 and x_2 , where $x_2 = x_1 + \Delta x$. An electromagnetic shaker (Bruel and Kjaer Type 4810) drives a shaft which vibrates in the plane of and parallel to the ultrasound beam axis at a radian frequency ω . This motion generates a $+x$ going shear wave of the form $Ae^{j(\omega t - kx + \theta)}$, where A is the wave amplitude, k the wavenumber ($k = 2\pi/\lambda$), and θ an arbitrary phase shift between the drive voltage and induced displacement. The shear wave induced displacements at locations x_1 and x_2 are $s_1(t) = A_1 e^{j(\omega t - kx_1 + \theta)}$ and $s_2(t) = A_2 e^{j(\omega t - kx_2 + \theta)}$. Neglecting shear wave attenuation, the displacement signals at the two locations differ by only a phase shift, and $s_2(t) = e^{-jk\Delta x} s_1(t)$. The phantoms were large enough to avoid standing wave generation at the frequencies (400–600 Hz) employed in the measurements.

Tracking echoes were not acquired simultaneously from both locations. Rather, pulses were fired and echoes collected in an alternating sequence, so that the time between echoes collected at one location was twice the pulse repetition period of $T = 128 \mu s$. Cross correlation tracking of the echo signals (identical to that used for estimation of SMURF induced displacements) yielded discrete-time estimates of position $\hat{s}_1[n] = s_1(2nT)$ and $\hat{s}_2[n] = s_2((2n + 1)T)$. Signals $\hat{s}_1[n]$ and $\hat{s}_2[n]$ are related by

$$\hat{s}_2[n] = e^{-jk\Delta x} s_1((2n+1)T) \quad (7)$$

$$= e^{-jk\Delta x} e^{j(\omega(2n+1)T - kx_1 + \theta)} \quad (8)$$

$$= e^{-j(k\Delta x - \omega T)} \hat{s}_1[n]. \quad (9)$$

The phase lag ϕ of $\hat{s}_2$ relative to $\hat{s}_1$ is $\phi = k\Delta x - \omega T$, where the $k\Delta x$ term is due to wave propagation and the $-\omega T$ term is due to the time delay T between acquisitions at x_1 and x_2 . Using the identity $k = 2\pi/\lambda$, the shear wavelength can be expressed in terms of the known quantities ω and T and the measured ϕ :

$$\lambda = \frac{2\pi\Delta x}{\phi + \omega T}. \quad (10)$$

Substitution of the estimated wavelength and drive frequency into Equation 1 yields the modulus estimate.

Sonoelastographic measurements were performed from 400 Hz to 600 Hz in 50 Hz increments. The frequency range was selected as high enough to allow shear wave attenuation to prevent standing wave generation, while low enough to allow adequate sampling given the pulse repetition frequency used. For each measurement 500 echoes were acquired at each location (x_1 and x_2). Two approaches were taken to generate estimates of modulus. To produce estimates of the modulus of uniform phantoms, the estimated phase over a 1.9 cm window was averaged to produce a single phase shift estimate. This phase shift was then used to produce a single modulus estimate at a given frequency. Averaging the phase estimate before calculation of modulus reduces the sensitivity of the estimate to noise in the phase estimate in the denominator of Equation 10. To produce estimates of modulus as a function of depth, phases were calculated for each sample of the RF echo signal and converted directly to a modulus estimate.

3.4. Unconfined compression

Uniaxial unconfined compressive testing was conducted on an MTS materials testing machine (Model 1/S, MTS Systems Corp, Eden Prairie, MN). A 5 N load cell (MTS Systems Corp) or 50 N load cell (MTS Systems Corp) was used for each sample, as appropriate for the estimated stiffness of the material. Zerdine samples were removed from the sample holders for mechanical testing but otherwise unaltered. Cores were cut from the gelatin phantoms using a custom designed aluminum trephine with a 30.0 mm inner diameter. A knife and custom designed knife guide were used to cut off the ends of each core to ensure a smooth square cut. The number of core samples cut from each phantom was dependent on the original phantom size and varied from 3 to 9. During testing, all samples were kept covered to prevent dehydration and maintained at room temperature. Preparation of the cores and compressive testing of the gelatin phantom samples took place within 8 hours of the SMURF and sonoelastography measurements. The Zerdine samples were tested immediately after removal from the provided sample holders. Prior to testing, the height and diameter of each cylindrical sample was measured using a ruler. The samples were placed on polished aluminum platens that were lubricated with cooking oil in order to minimize friction between the phantom and platens.

The MTS testing machine was controlled using Testworks software (Version 3.10, MTS Systems Corp). Prior to testing, 5% pre-strain was manually applied followed by 9 cycles of pre-conditioning to 10% final strain. Data was collected for one cycle of compression to 10% final strain for each sample at a deformation rate of 0.5 mm/sec. Force-deformation data was obtained from Testworks, then exported to Microsoft Excel 2002 for analysis. Stress (σ) and strain (ϵ) were calculated by normalizing force by area and deformation by the initial height of each core. Young's modulus (E) was determined by the slope of the stress/strain graph from 5% to 9% loading strain. The Young's modulus was converted to shear modulus using the relationship $G = E/2(1 + \nu)$ assuming a Poissons ratio (ν) of 0.5.

4. Results

4.1. Overall phantom moduli

Measurements of the average modulus of the gelatin and Zerdine phantoms were obtained by SMURF and unconfined compression. Additionally, measurements of average modulus were made on the gelatin phantoms using sonoelastography. The goal of the overall measurements

was to verify the accuracy of the SMURF method in relation to a standard mechanical test (unconfined compression) and, for the gelatin phantoms, a dynamic, shear wave based method.

Combined overall measurements of the two gelatin phantoms are shown in figure 6. The sonoelastographic values were calculated using the average phase shift calculated over a 1.7 cm axial window. The values given in each case represent the average over five trials from 400 Hz to 600 Hz. The SMURF results represent the average over all trials within the 8 mm region of interest about the push-beam focus. Five trials were averaged for the stiff phantom; six trials were averaged for the compliant phantom. Push and track beams were focused at 2 cm, and a push-beam spacing of 1.95 mm was used. Tracking of the radiation-force induced shear wave was performed along a single A-line parallel and 0.45 mm to the left of the leftmost push beam axis. The frequency estimate at each depth sample was converted to a modulus estimate. These modulus estimates were then averaged over the 8 mm depth of field. The unconfined compression results are the average of values obtained from 30 mm diameter cores cut from the original phantom. Three cores were cut from the compliant phantom, nine from the stiffer phantom. The unconfined compression measurements tended to be larger than the values given by Sono and SMURF and have higher variance. This is due, at least in part, to the difficulties encountered in cutting the core samples from the original phantom. The soft phantom material deformed slightly during cutting, resulting in samples that were not uniformly cylindrical and complicating accurate measurement of their dimensions. Nevertheless, results for both phantoms by all three measurements agree within ± 1 standard deviation of the results of the respective methods. The close agreement with the sonoelastographic method in particular suggests an absence of systematic bias in the SMURF implementation.

Overall estimates of the moduli of the four Zerdine samples by SMURF and unconfined compression are shown in figure 7. SMURF estimates were acquired using push and tracking beams focused at a depth of 1.5 cm, with motion tracked along a single A-line 0.45 mm to the left of the leftmost push beam axis. Three acquisitions were made at each of three locations in each sample, for a total of nine acquisitions per sample. The mean modulus estimate over a depth range of 1 to 1.5 cm was averaged over the three trials to produce the overall estimate at a given location. SMURF estimates of modulus show good agreement with those obtained by unconfined compression.

4.2. Estimates of modulus vs depth

Estimates of shear modulus as a function of depth obtained by SMURF at two locations in the compliant gelatin phantom are plotted in figure 8. The estimates represent the value obtained by tracking along a single A-line 0.45 mm to the left of the leftmost push beam axis over a time range of 0.4 to 4.0 ms after the transmission of the first push beam. Push beam spacings of 1.5 mm and 1.95 mm were used. The measurements were repeated three times at each location for each push beam spacing. The standard deviation of the trial-trial estimate are illustrated, and are comparable to the variation over the range of depths examined. The statistics of each trial are listed in tables 1 and 2 for the 1.5mm and 1.95mm push beam cases, respectively. While the figures cover a depth range of 1.45–2.1 cm ($\lambda_s = 1.5$ mm) or 1.2–1.95 cm ($\lambda_s = 1.95$ mm), the tables report data for the intersection of these regions. The trial-to-trial standard deviation is comparable to the variation within the depth of field, suggesting that the estimates are limited by random fluctuations, i.e. tracking jitter due to echo SNR, rather than a systematic, correlated noise source.

The estimated shear modulus over a function of depth using sonoelastography is shown in figure 9. The plot represents the average modulus estimated over three trials, tracked at a single location, with error bars representing the trial-to trial variation. Each trial consisted of an 150 echo sequence, so that 15 cycles (at 400 Hz) to 23 cycles (at 600 Hz) were used for phase estimation. The peak-to-peak displacement amplitude was approximately 16 μm . In contrast

to the SMURF results, the random error component is insignificant compared to the variation within the region of interest, suggesting a correlated noise source dominates over echo SNR in determining the variance of the estimated modulus. The contrast between the SMURF and sonoelastography noise sources is examined in the Discussion section.

While SMURF estimates of shear modulus may be obtained by tracking at a single location as shown above, a reduction in the variance of the estimate may be obtained by averaging modulus estimates obtained at more than one tracking location. To illustrate, estimates of shear modulus as a function of depth for the compliant gelatin phantom are plotted in figure 10 for the same two locations as in figure 8. These estimates were obtained by tracking at five A-lines spanning a 0.6 mm lateral window centered 0.4 mm to the left of the leftmost push beam. The shear modulus estimates are first calculated independently at each depth and A-line. The estimates at same depth sample for each of the five A-lines are then averaged to produce a single modulus estimate for that depth. As can be seen by comparing figures 8 and 10 both the trial-to-trial variation, and the overall variation at a given location, of the SMURF estimate are reduced though averaging. The average trial-to-trial variation is reduced from 3% for the single location case to 1%.

Estimates of shear modulus as a function of depth for the four uniform Zerdine samples are shown in figure 11. Estimates made by tracking at a single lateral location 0.45 mm to the left of the leftmost pushing beam axis are shown in figure 11a. Figure 11b depicts modulus estimates at the same push locations, where the modulus value at each depth is the average of estimates at five lateral locations spanning a 0.6 mm width. Both the trial-to-trial variance and the average variation over 5.5 mm region of interest are significantly reduced by averaging.

5. Discussion

The results presented demonstrate excellent agreement between SMURF and established methods for shear modulus estimation. Overall shear modulus estimates in the gelatin phantoms by SMURF and sonoelastography agree to within a standard deviation of the measurement variation. Measurements over a range of moduli in the Zerdine phantoms indicate the ability to quantify shear modulus with a precision of a few percent of the modulus. This suggests that clinically significant variations in shear modulus could be resolved with SMURF.

As discussed in the introduction, a key difference between SMURF and other methods for estimating shear modulus is that SMURF modulus estimates derive from displacement tracked along a single A-line. SMURF uses multiple push beams (delivered sequentially as here, or simultaneously as in [1]) to estimate the modulus of the material between the push beams. Other methods, including the sonoelastographic method used here, rely on tracking at two adjacent locations to estimate wave shear wave speed between two points.

Tracking of shear wave propagation at any given location is subject to jitter error due to a combination of random noise (SNR) and structured or coherent error, due to shearing effects [14]. While uncorrelated noise may be removed by repeated trials and averaging, correlated noise is, by definition, not removed through averaging. In the case of SMURF estimation, shear waves of a known wavelength propagate past an observation point. Any distortion in tracking the peak first wave is mirrored in tracking the next. Thus, estimation of the time *between* wave crests is not subject to correlated noise. The measurement made is differential, and any systematic bias is subtracted out in the time difference calculation. Correlated errors in SMURF derive from errors in the assumed wavelength of the shear wave. Such errors can arise due to variations in radiation force due to variations in absorption coefficient of the material, and due to beam distortion due to refraction or phase aberration errors.

In contrast, methods relying on measurements of shear wave arrival time or phase at two locations, like the sonoelastographic measurement method described here, are subject to bias errors at each tracking location. The bias arises both from shearing effects, and from the presence of speckle. Displacement tracking along a given A-line is biased by the presence of strong scatterers. Scatterers whose echoes interfere coherently at a point slightly off the beam axis, like a bright off axis speckle, will be tracked in preference to scatterers precisely on the beam axis which interfere destructively, producing a weak echo. These biases have the effect of extending or shortening the assumed path length Δx between the two observation points. Because a different distortion or bias is introduced in the tracking at each location, errors of this type are not removed when the phase difference is calculated.

The difference in tracking at a single location versus two locations is illustrated in figure 12, which plots a sample of the phase shift measured for three values of Δx in the compliant gelatin phantom as a function of depth. Error bars on each trace illustrate the small (< 0.005 radian) variation in the phase estimate over three trials, an indication of the (small) SNR related component of the error in the phase estimate. Tracking at a single location ($\Delta x = 0$ and estimating phase using the $s_1[n]$ and $s_2[n]$ signals described in the Methods section yields a phase estimate with a standard deviation over the region of interest comparable to the random error. In contrast, tracking at two lateral locations separated by more than the two-way beamwidth laterally ($\Delta x = 0.885$ mm and $\Delta x = 1.77$ mm) yields similarly repeatable measurements with much higher variation over the region of interest — standard deviations of 0.33 and 0.28 radian, respectively. The covariance of the difference between the phase shift at the two locations accounts for half of the total variations, consistent with the shared track location x_1 . Suppression of the correlated noise requires averaging phase shift measurements over a lateral window, as described by Palmeri et al.[22]. The use of lateral averaging can be expected to decrease lateral spatial resolution.

A potential limitation of SMURF is that it provides modulus information only within the spatially modulated region of the push beam. The axial range over which a particular spatial modulation can be generated is limited for geometrically focused beams. This limits the useful axial range for a particular push beam ensemble to the focal zone. Methods which track the propagation of a single shear wave (e.g. [22,23]) can follow the lateral propagation of the shear wave to determine shear modulus over an area larger than the push beam. The potentially smaller number of required push beams could result in reduced the tissue heating due to push beam absorption as compared with SMURF. The trade-off between the need for a greater number of push beams and the improved speckle noise suppression of SMURF versus other methods in terms of thermal effects is not obvious and merits further study.

The results presented here are limited to homogeneous, elastic phantoms. The density of the material is assumed to be known and uniform. Deviations from the assumed value would result in an inaccurate estimate of modulus. While soft tissues are not of uniform density, the range of densities encountered in the body (from 0.94 g/ml for fat to 1.07 g/ml for muscle [31]), is small compared with the variations in shear modulus between tissues. Thus, the error in modulus estimate due to density variation is expected to be small compared with the real variations in shear modulus. Spatially varying modulus may be resolved with SMURF, as the modulus estimate depends only on the modulus of the material within the push beam [1]. Modulus variations on the scale of the push beam ensemble width or larger should therefore be resolvable. Preliminary results support this conclusion [25]. Viscoelastic effects were negligible in the phantoms studied here, while tissue may be expected to exhibit significant frequency dependence in modulus. Distortion of the induced shear wave due to dispersion could alter the estimated shear modulus, as well as complicate shear wave generation. On the other hand, changes in the observed shear wave propagation due to material property deviations from the perfectly elastic case may prove useful for tissue characterization.

6. Conclusion

We have presented a new algorithm for calculation of shear modulus using SMURF. This method relies on the autocorrelation of the radiation force induced material velocity signal to estimate the period of the shear wave. In combination with the known spacing between push beams (“wavelength”) the shear modulus is estimated. Measurements in phantoms with shear moduli ranging from 2.5kPa to 18kPa show good agreement between SMURF and established methods: unconfined compression and sonoelastography.

The results presented also indicate a major advantage of the SMURF method, namely that tracking at a single location greatly reduces the error introduced by decorrelation and speckle in the tracking process, in contrast to sonoelastography. The measurement of tissue motion at a single location eliminates uncertainty due to correlated source jitter, as any non-random error is repeated with each cycle of the shear wave. The period of the shear wave signal, which SMURF relies on to generate its estimate, is unaffected. These results suggest that SMURF may allow high-resolution estimates of shear modulus to be generated, since averaging over a large area is not needed to obtain a modulus estimate. Future work will examine this aspect in detail.

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Figure 1.

Schematic illustration of a SMURF ensemble. The pulse sequence proceeds from left to right. Two “reference” echoes are acquired from the tracking location, prior to the push pulse sequence, using a two-cycle-long B-mode style pulse. Three weakly focused, 200 cycle-long “push” beams are transmitted $79\ \mu\text{s}$ and $1.5\ \text{mm}$ or $1.95\ \text{mm}$ apart. Sixty “tracking” echoes are then acquired at the sample location as the reference echoes. The location of the reference and tracking echoes may be changed from one ensemble to the next to synthesize a movie of shear wave propagation.

(A)

(B)

Figure 2. Simulated push beam intensity plots in media with attenuation coefficients of (A) 0 dB/cm/MHz and (B) 0.5dB/cm/MHz. Simulations modeled the Siemens VF10–5 transducer radiating 200 cycle, 6.67 MHz beams. Sequences with 1.95 mm spacing used unshaded F/4.3 apertures, while those with 1.5 mm spacing beam used an F/3.3 aperture.

Figure 3.

Illustration of autocorrelation processing for frequency estimation. (A) Material velocity over a axial range of 1.4 to 2.1 cm for a time range of 0.3 to 5ms after application of the first of three push pulses. Velocity is indicated by the grayscale, with white representing a velocity of 1 mm/s away from the transducer, black 1 mm/s towards it. (B) A sample velocity versus time trace taken at a depth of 17mm. (C) The autocorrelation of the trace in (B).

Figure 4.

Space-time graph depicting the propagation of three wave peaks generated by a sequential-push ensemble. The dashed, dotted, and solid lines represent the shear wave peaks associated with the first, second and third focused push beams within the ensemble. Each wave crest propagates from its origin at a rate c , thus the slope of each line is $\pm 1/c$. The time T between push beams, exaggerated here for clarity, leads to an increase of cT in effective shear wavelength for $-x$ -going waves and an identical decrease for $+x$ going waves.

Figure 5. Schematic illustration of the setup for sonoelastography data acquisition. The shaker drives a rod coupled by pressure to one side of the phantom, generating a shear wave that radiates to the right. Ultrasound echoes are acquired at locations x_1 and x_2 at a pulse repetition frequency of 3.9kHz. Acquisitions at each location are separated in time by 128 μ s.

Figure 6.

Estimates of shear moduli of two uniform gelatin-based phantoms. Unconfined compression measurements were performed on 3cm diameter cores cut from phantoms. Error bars indicate ± 1 standard deviation of the measurements of all core samples. Sono measurements represent the average of 5 measurements taken over a 400–600 Hz range in 50 Hz steps, with the modulus calculated from the average phase shift over 1.7 cm axial window. The indicated standard deviation is the over the five frequencies evaluated. The SMURF measurements represent the mean modulus calculated over a 0.8 cm window within the focal region of the push beams. The standard deviation is that of the means at different locations within the phantom. Five locations were measured once each in the stiff phantom; two locations were measured three times each in the compliant phantom. The push beam spacing used was 1.95 mm.

Figure 7.

Shear modulus estimates of Zerdine samples. SMURF bars represent the mean modulus averaged over an 5 mm axial window near the focus. Error bars depict the ± 1 standard deviations of the modulus calculated over the 5mm window. Unconfined compression error bars indicate the estimated uncertainty in the modulus measurement due to sample dimension uncertainty.

Figure 8.

Shear modulus versus depth estimates for the compliant gelatin phantom. (A,C) Mean estimated shear modulus vs depth at two separate locations within the phantom. Error bars, placed every 20th sample, represent standard deviation of the estimate, based on three repeated trials at this location. The push beam spacing was 1.5mm for these measurements. (B,D) are shear modulus estimates taken at the same locations as (A,C), respectively, using a push-beam spacing of 1.95mm.

Figure 9. Sonoelastography-derived shear modulus estimate as a function of depth in the compliant gelatin phantom. Error bars represent the trial-to-trial standard deviation over three measurements at the same location.

Figure 10.

SMURF shear modulus versus depth estimates for the compliant gelatin phantom obtained by averaging modulus estimates at five tracking locations. The modulus estimate at each depth is the result of averaging modulus estimates at that depth obtained from five lateral tracking locations spanning a 0.6mm lateral window. Error bars represent the ± 1 standard deviation range of three repeated trials at each location. (A) First location: $\bar{G} = 1.90\text{kPa}$, average trial-to-trial standard deviation = 0.023kPa or 1.20%. (B) Second location: $\bar{G} = 1.99\text{kPa}$, average trial-to-trial standard deviation of 0.013kPa, or 0.65%

Figure 11.

SMURF estimates of shear modulus of four Zerdine samples versus depth. (A) Estimates obtained using tracking at a single location 0.45 mm to the left of the leftmost pushing beam, with a push beam spacing of 1.95 mm. Error bars represent the standard deviation over three trials at a single location. (B) Same location as (A), but estimates obtained by averaging modulus estimates over a 0.6 mm lateral window. The average trial-to-trial standard deviation is reduced from 5.2% to 2.3% with averaging. The noise reduction factor is approximately $\sqrt{5}$, consistent with an independent random noise source as the dominant source of error.

Figure 12.

Sonoelastographic phase difference estimates in the compliant gelatin phantom for three track beam spacings. The mean phase estimates are 0.3816 ($\Delta x = 0\text{mm}$), 2.328 ($\Delta x = 0.885\text{mm}$), and 4.342 ($\Delta x = 1.77\text{mm}$) radian. The intertrial standard deviations were 0.0026, 0.0040, and 0.0043 radian, respectively. The intratrial standard deviation — the standard deviation of the phase shift estimates over depth (total of 1.9cm) — was much smaller for the $\Delta x = 0$ case (0.0021) than for $\Delta x = 0.886\text{mm}$ (0.3328) and $\Delta x = 1.77\text{mm}$ (0.2810). The small trial-to-trial variation in phase estimate compared to the overall variation in the estimates suggests the variation is not due to inadequate SNR.

Table 1

Compliant gelatin phantom data for $\lambda_s = 1.95\text{mm}$. Mean and standard deviation (in parenthesis) of shear modulus estimates (in kilopascals) at two locations, three trials at each location, over a depth range of 1.45 to 1.95 cm. Data in the “combined” column represents the mean over the three trials, and the intersample standard deviation, calculated as the average of the standard deviation of each sample point over the three trials.

location	trial 1	trial 2	trial 3	combined
1	1.90 (0.04)	1.91 (0.07)	1.92 (0.10)	1.91 (0.06)
2	2.05 (0.06)	2.03 (0.05)	2.03 (0.06)	2.03 (0.05)

Table 2

Compliant gelatin phantom data for $\lambda_s = 1.5\text{mm}$. Mean and standard deviation (in parenthesis) of shear modulus estimates (in kilopascals) at two locations, three trials at each location, over a depth range of 1.45 to 1.95 cm. Data in the “combined” column represents the mean over the three trials, and the intersample standard deviation, calculated as the mean of the standard deviation of the modulus estimates at each sample point over the three trials.

location	trial 1	trial 2	trial 3	combined
1	1.80(0.03)	1.82 (0.04)	1.77 (0.03)	1.80 (0.02)
2	1.94(0.04)	1.92 (0.03)	1.91 (0.03)	1.92 (0.02)