Published in final edited form as:

Phys Med Biol. 2017 February 07; 62(3): 1149–1171. doi:10.1088/1361-6560/aa51ac.

An Analysis of Intrinsic Variations of Low-frequency Shear Wave Speed in A Stochastic Tissue Model: The First Application for Staging Liver Fibrosis

Yu Wang¹, Min Wang², and Jingfeng Jiang¹

¹Department of Biomedical Engineering

²Department of Mathematical Sciences, Michigan Technological University

Abstract

Shear wave elastography (SWE) is increasingly being used to noninvasively stage liver fibrosis by measuring shear wave speed (SWS). This study is to quantitatively investigate intrinsic variations among SWS measurements obtained from heterogeneous media such as fibrotic livers. More specifically, this preliminary study aims to demonstrate that intrinsic variations in the SWS measurements, in general, follow a non-Gaussian distribution and are related to heterogeneous nature of the medium being measured. Using the principle of Maximum Entropy (ME), our primary objective is to derive a probability density function (PDF) of the SWS distribution in conjunction with a lossless stochastic tissue model. Our secondary objective is to evaluate the performance of the proposed PDF using Monte-Carlo (MC) simulated shear wave data and against three other commonly used PDFs.

Based on statistical evaluation criteria, initial results showed that the derived PDF fits better to MC-simulated SWS data than other three PDFs. It was also found that shear wave (SW) fronts stabilized after a short (as compared to the SW wavelength) travel distance in lossless media. Furthermore, in lossless media, the distance required to stabilize the SW propagation was not correlated to the SW wavelength at low frequencies investigated (*i.e.* 50 Hz, 100 Hz, and 150 Hz). Through examining MC simulation data, our preliminary results suggested that elastic (shear) wave scattering became more pronounced when the volume fraction of hard inclusions increased from 10% to 30%.

In conclusion, using the principle of ME, we theoretically demonstrated that SWS measurements in this model follow a non-Gaussian distribution for the first time. Preliminary data indicated that the proposed PDF can quantitatively represent intrinsic variations in SWS measurements simulated using a two-phase random medium model. Advantages of the proposed PDF are its physically meaningful parameters and solid theoretical basis.

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, jjiang1@mtu.edu.

Keywords

Monte-Carlo simulations; principle of maximum entropy; random medium; shear wave; shear wave elastography

Introduction

Liver fibrosis refers to a clinical condition where excessive connective tissue builds up in the liver (Birbrair *et al.*, 2014). Early stage liver fibrosis most often goes completely unnoticed, whereas late stage liver fibrosis (*i.e.* cirrhosis) are often fatal. The severe consequences of the progression of liver fibrosis, the common occurrence of liver fibrosis in the adult population (1-2%), the lack of reliable methods to screen patients at high risk, and the benefit to clinical outcomes from early detection, combine to motivate the continued search for a non-invasive method which would clinically assess the stage of liver fibrosis (Barr *et al.*, 2015). Measuring shear wave speed (SWS) using ultrasound-based Shear Wave Elastography [SWE] (Sarvazyan *et al.*, 1998; Nightingale *et al.*, 2003; Bercoff *et al.*, 2004) or Transient Elastography [TE] (Sandrin *et al.*, 2003), has emerged as a potential clinical metric for staging liver fibrosis (Ferraioli *et al.*, 2015). This is because fibrotic liver tissues are progressively hardened and the local tissue “stiffness” is often correlated to liver fibrosis stages. In the framework of ultrasound SWE, an acoustic pulse is first transmitted to produce shear waves (SW), which propagate laterally from the direction of the acoustic pushing pulse, whereas TE uses an external mechanical vibrator to induce shear waves. Then, the shear waves can be tracked with a sequence of ultrasound echo data (*e.g.* radiofrequency data) in order to estimate SWS and, the estimated SWS is related to the tissue shear modulus (Bamber *et al.*, 2013). Initial clinical successes of SWE and TE for staging liver fibrosis have been well documented (Ferraioli *et al.*, 2014). The apparent potential for SWE and TE has resulted in several major vendors (*e.g.*, General Electric, Siemens, Supersonic Imagine, Echosens, *etc.*) releasing commercially available packages that utilize ultrasound to measure SWS. It is worth noting that laboratory blood tests are not ready to serve as a screening tool to differentiate at least four liver states: fatty liver, normal liver, fibrotic liver and mixed fatty/fibrotic liver (Mofrad *et al.*, 2003; Parkes *et al.*, 2006; Friedrich-Rust *et al.*, 2010; Carey and Carey, 2010).

However, some potential problems of SWE and TE have been identified while being used for staging liver fibrosis. A couple of studies of TE (Castera *et al.*, 2010; de Ledinghen *et al.*, 2012) found that the rate of unreliable results was still relatively high (up to 17%). Results were determined as “unreliable” by the authors (Castera L, 2010) if one of the following three conditions met: (1) there were fewer than 10 valid shots, (2) an interquartile range (IQR) among all results was greater than 30% and (3) a success rate was less than 60%. Another study (Goldschmidt *et al.*, 2013) reported that there was a 10% unsuccessful rate when TE was used to measure liver stiffness in children younger than 6. In one clinical study (Cassinotto *et al.*, 2014) involving supersonic shear imaging (a variant of SWE), the average failure rate was about 10.4% and the rate of unreliable measurements was considerably higher (26-28%) in obese patients (body mass index ≥ 30 kg/m²). Furthermore, other results also showed that SWE may not be able to differentiate fibrosis from significant steatosis

(Wieckowska and Feldstein, 2008; Rockey and Bissell, 2006). Furthermore, SWS measurements could also be system-dependent. For instance, recent results published by the Quantitative Imaging Biomarker Alliance (QIBA), a research consortium under the Radiological Society of North America (RSNA), have shown that there was a statistically significant difference in the SWS estimation among systems and with depth in the same phantom (Timothy J Hall, 2013). In short, it is our belief that those early results indicated that more work is needed in order to gain confidence in clinical interpretations of SWE results.

To address this demand from the clinical community, it is important to understand, and hopefully quantify, the uncertainty of SWS, which is not fully understood at this point. It is logical to assume that the uncertainty in SWS measurements of fibrotic liver tissues largely stems from two sources: measurement errors and intrinsic variations of SWS distribution. Measurement errors are defined as errors induced in the process of estimation of SWS from ultrasound data. Therefore, measurement errors include errors induced by speckle tracking and noise from the recorded ultrasound data, among others. Measurement biases and variances in SWS have been studied by several groups. Thomas Deffieux (Deffieux *et al.*, 2012), based on estimation theory, theoretically established the relationship among the estimated shear modulus and system parameters such as noise, frequency components of the propagating SW, *etc.* Biases among SWS measurements were experimentally investigated by Zhao *et al.* in tissue mimicking materials (Zhao *et al.*, 2011). Now referring to intrinsic variations in SWS measurements, we define the intrinsic variations as dispersions among SWS measurements due to the fact that fibrotic liver tissues are heterogeneous and complex. Our preliminary objective of this study is to derive a probability density function (PDF) of SWS that statistically represents the above-mentioned intrinsic variations of SWS measurements. Since the underlying stiffness distribution of fibrotic liver tissues cannot be precisely obtained, we model the fibrotic liver tissue as a stochastic two-phase medium consisting of two components: normal liver parenchyma and over-expressed connective tissues. As a first approximation, we assume that those over-expressed connective tissues are randomly embedded in the normal liver parenchyma (Robbins *et al.*, 2010). In short, the proposed PDF will be derived in conjunction with a stochastic two-phase tissue model that is only characterized by relative volume fractions of those two (phase) components — normal liver parenchyma and over-expressed connective tissues.

In this preliminary study, we used a combined theoretical and computational approach. Such a study, to our knowledge, has not been reported in the SWE and TE literature yet. The remainder of this paper is structured as follows. In the Methods and Materials Section, a PDF for SWS distribution in stochastic tissue models is derived by using the principle of Maximum Entropy (ME) (Jaynes, 1957b, a). The derived PDF is a theoretical basis for quantification of the intrinsic variations of SWS in the heterogeneous liver tissues. Additional information related to the creation of the proposed stochastic tissue model, statistical evaluation criteria and Monte-Carlo (MC) simulations using an open-source simulator (K-Wave) (B. Treeby, 2012; Bradley E. Treeby, 2014) is also provided in this section. In the Results Section, the derived PDF is evaluated using MC-simulated SW data and against three other commonly-used PDFs (*e.g.* Gaussian distribution, generalized

Gaussian distribution and log-normal distribution). Some additional observations, as well as closing remarks, are described in the Discussions and Conclusion Sections.

Materials and Methods

As illustrated in Figure 1, the proposed work is centered at the derivation of the proposed PDF of the SWS using the principle of ME (Section A). In order to validate the derived PDF, MC-simulated SW propagation data (Section C) from two-phase media were used in conjunction with statistical (model) evaluation methods (Section B).

A. Derivation of Probability Density Function (PDF)

Consider an elastic (lossless) heterogeneous medium, which consists of multiple isotropic non-overlapping phases with elastic bulk moduli (K_i), shear moduli (G_i), mass density values (ρ_i) and the volume fractions of each phase (c_i ; $\sum c_i = 1$). The subscripts i denotes phase index, respectively. For simplicity, the multi-phase medium can be effectively treated as isotropic and macroscopically homogeneous. Therefore, this medium which can be characterized by effective bulk modulus (K), effective shear modulus (G) and effective mass density (ρ). Consequently, given a medium, K and G are two unknown random variables. Among most biological soft tissues, variations in mass density are small as compared to those in the shear modulus (Duck, 1990). We treat the effective mass density ρ as a constant to simplify the derivation.

Formally, we now assume that an arbitrary multi-phase medium can be specified by a set of physical properties $J = (K_i, G_i, \rho_i, c_i)$. Given the multi-phase medium whose properties can be specified by the set J , under the framework of effective medium theory, the macroscopic SWS of the medium (V_s) can be related to the effective shear modulus G by (Wells and Liang, 2011; Doherty *et al.*, 2013),

$$V_s = \sqrt{\frac{G}{\rho}} \quad (1)$$

where ρ is the effective mass density. Eqn. (1) is only valid with low-frequency shear wave propagation in elastic (lossless) media.

In information theory, Jaynes' information entropy (H) (Jaynes, 1957b) of the effective shear modulus G is given below,

$$H = - \int_{-\infty}^{+\infty} p(G) \ln \frac{p(G)}{m(G)} dG \quad (2)$$

where $m(G)$ can be used to represent *a priori* information and $p(G)$ is a (histogram) distribution of G . Based on the principle of ME, the Jaynes' entropy H reaches its maximum if $p(G)$ reflects the data distribution in the best possible way, given the *priori* information

$m(G)$. Consequently, maximization of H leads to an optimized $p(G)$ that best describes the given data G . In Eqn. (2), $m(G)$ has been set to 1, meaning that no *prior* information regarding the distribution of G is available to us.

To ensure that the optimized $p(G)$ is a good fit of the given data G , the maximization of H has to be constrained by the statistical moments of the data G as follows,

$$\int_{-\infty}^{+\infty} p(G) dG = 1 \quad (3)$$

$$\int_{-\infty}^{+\infty} p(G) G dG = G_E \quad (4)$$

$$\int_{-\infty}^{+\infty} p(G) (G - G_E)^2 dG = G_D \quad (5)$$

where G_E and G_D are mean and variance of the effective shear modulus G . It is important to note that G is a random variable and, now $p(G)$ becomes the PDF of the given effective modulus data G . A Lagrange multiplier method (Bertsekas, 1995) was used to maximize H in conjunction with Eqn. (1). This process yields an analytical expression of PDF of the macroscopic SWS (V_s),

$$p(V_s) = \frac{1}{\sqrt{2\pi G_D}} e^{-\frac{(V_s^2 \rho - G_E)^2}{2G_D}} 2\rho V_s \quad (6)$$

A complete derivation of Eqn. (6) is provided in Appendix A.

B. Model Evaluation

The derived PDF, $p(V_s)$, was compared with three commonly used PDF functions (*Section B.1*) to demonstrate its fitness to simulated SWS data. As an integral part of this evaluation process, statistical model selection criteria (*Section B.2*) will be used as quantitative metrics to determine the performance.

B.1 Commonly-Used PDFs—Three commonly-used PDFs (Casella and Berger, 1990) (*i.e.* Gaussian distribution, log-normal distribution and generalized Gaussian distribution) were selected to compare with the theoretically-derived PDF (*i.e.* Eqn. (6)). The PDF of *Gaussian distribution* (GAD) can be written as follows,

$$p^{\text{GAD}}(V_s) = \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{(V_s - \mu)^2}{2\sigma^2}} \quad (7)$$

where μ and σ are the mean and standard deviation of SWS, respectively.

The PDFs of *log-normal distribution* (LND) and *generalized Gaussian distribution* (GGD) are expressed as follows, respectively,

$$p^{\text{LND}}(V_s) = \frac{1}{V_s \sigma \sqrt{2\pi}} e^{-\frac{(\ln V_s - \mu)^2}{2\sigma^2}} \quad (8)$$

$$p^{\text{GGD}}(V_s) = \frac{\beta}{2\alpha\Gamma(1/\beta)} e^{-(|V_s - \mu|/\alpha)^\beta} \quad (9)$$

Similarly, in Eqn. (8), μ and σ are the mean and standard deviation of $\ln(V_s)$, where $\ln()$ is a natural logarithm function, while μ is the mean of V_s in Eqn. (9). In Eqn. (9), β is estimated by using a Newton-Raphson iterative procedure (Ryaben'kii and Tsynkov, 2007). Once β is

obtained, α can be evaluated as $(\frac{\beta}{N} \sum_{i=1}^N |V_{si} - \mu|^\beta)^{\frac{1}{\beta}}$, where N is the number of samples.

B.2 Statistical Model Selection Criteria—Two commonly used model-comparison criteria, namely the Akaike Information Criterion (AIC) (Akaike, 1973) and the Bayesian Information Criterion (BIC) (Findley, 1991), were used to evaluate the relative quantity and fitness of the four statistical PDFs (*i.e.* Eqns. (6)-(9)). Let $L = \prod_{i=1}^n p(V_{si})$ be the likelihood function of any of those four statistical PDFs ($p(V_{si})$) and k be the number of estimated parameters in the PDF. Then the AIC and the BIC of a given distribution can be, respectively, presented as follows,

$$\text{AIC} = -2\ln(L) + 2k \quad (10)$$

$$\text{BIC} = -2\ln(L) + k \cdot \ln(n) \quad (11)$$

In general, when choosing from several models under consideration, the one with the lowest AIC and BIC is preferred in terms of data fitness.

C. Overall Workflow of Numerical Experiments

Data obtained from MC-simulated SW were generated to evaluate the derived PDF (see Eqn. (6)). As shown in Figure 2, the corresponding MC simulations involve two steps. In the first step, one cycle of a low-frequency (*i.e.* 50 Hz, 100 Hz and 150 Hz) plane [shear] wave excitation was prescribed and subsequently SW was induced. Excitations with a single fixed frequency are similar to ones used in TE. The chosen excitation frequency falls in the range of a typical SW frequency excited in a clinical setting: between 50 Hz and 200 Hz (Shiina *et*

et al., 2015). SW propagation was simulated by using K-Wave, an open-source wave simulator (B. Treeby, 2012). Details of K-Wave simulations including boundary conditions can be found in subsection E and Appendix B below. In the second step, a directional filter (Deffieux *et al.*, 2011) was first applied to simulated particle velocity data. Then, a lateral time-to-peak (TTP) algorithm (Palmeri *et al.*, 2008) was adopted to calculate SWS along the wave propagation direction at different depths based on “filtered” particle velocity data. The temporal sampling frequency of the recorded signals was approximately 100 KHz (Palmeri *et al.*, 2008).

D. Two-phase Fibrotic Liver Tissue Model

The proposed two-phase stochastic tissue model was designated to mimic histological characteristics of liver fibrosis from two important aspects: (1) the amount of fibrosis and (2) architectural changes due to fibrosis (Standish *et al.*, 2006). This was done under the framework of METAVIR classification (Bedossa and Poynard, 1996). A schematic illustration of the proposed stochastic tissue model can be seen in Figure 3 (a), where hepatocytes were arranged in lobules and each lobule was modeled as a hexagon. Each edge of those hexagons was approximately 1 mm (Stenvall *et al.*, 2012). Each septum, forming an edge of a lobule, was connected by portal triads. In the early stages of liver fibrosis (*i.e.* METAVIR scores F1 and F2), liver injuries occur and inflammatory cells migrate across endothelium of portal vessels. This process will initiate depositions of collagen. Thus, in the early stages, collagen will be deposited around portal tracts with extensions into adjacent peri-portal regions along septa, as shown in Figures 3(b)-(c) and those collagen depositions look like isolated islands (See Figure 3(b)-(c)). As the liver fibrosis progresses (*i.e.* METAVIR scores F3 and F4), inflammatory cells migrating across the endothelium of hepatic sinusoids can gain direct access to the liver parenchyma, thereby causing lobular inflammation. Consequently, fibrous expansions of most portal areas cause portal-to-portal bridging or portal-to-central bridging (Zalata, 2011), as shown in Figures 3(d)-(e). In other words, at the late stages of the liver fibrosis, deposited collagen “islands” (see Figures 3(b)-(c)) have been connected by septa and the overall architectural appearance looks more like a complex web (see Figure 3(e)). Overall, the proposed stochastic tissue model captures both the increasing presence of collagen content and spatial characteristics of collagen depositions, as shown in Figures 3(b)-(e).

An in-house MATLAB script (Mathworks Inc., MA, USA) was used to create tissue compositions that represent different fibrosis stages, given a volume fraction of collagen content. The selected volume fractions of collagen content were adopted based on measured values of collagen proportional area (CPA), as shown in Table 1 (Huang *et al.*, 2013). All necessary parameters needed for the simulations of SW propagation were based on data available in the literature. More specifically, shear moduli of the background (*i.e.* normal liver parenchyma) and the fibrotic inclusions (*i.e.* collagen) were set to 3.24 kPa (SWS = 1.8 m/s) (Kim *et al.*, 2012) and 400 kPa (SWS = 20 m/s) (Khamdaeng *et al.*, 2012; Seeram Ramakrishna, 2004), respectively. The mass density of the background and the fibrotic inclusions were set to be 1000 kg/m³ and 1200 kg/m³ (Duck, 1990), respectively. The compressional sound speed of the background and the fibrotic inclusions were set to be 1540 m/s and 2000 m/s (Duck, 1990), respectively.

In order to assess sizes of those inclusions with complex shapes (see Figures 3(b)-(e)), correlation lengths were calculated based on two-point correlation function (Torquato, 2002). Mathematically, a two-point correlation function $S(r_1, r_2)$ between two arbitrary points p_1 and p_2 is defined as follows,

$$S(p_1, p_2) = \langle I(p_1)I(p_2) \rangle \quad (12)$$

where angular brackets denote an ensemble average, and $I(p)$ is defined as

$$I(p) = \begin{cases} 1, & \text{if } p \text{ is in the inclusion phase} \\ 0, & \text{otherwise} \end{cases} \quad (13)$$

Equation (12) represents a probability of finding two points p_1 and p_2 in the same phase separated by a distance r . Consequently, the correlation length is defined as the distance by which the correlation drops to a stable plateau.

E. Performing 2D SW Simulations

A uniform 90 mm (along the wave propagation direction) $\times$ 22 mm computing domain was used to generate MC simulated SW propagation data, as shown in Figure 4. A 20 mm $\times$ 20 mm central rectilinear region of interest (ROI) containing either 10% or 30% inclusions was embedded into the computing domain. In this study, 10% and 30% inclusions were chosen for early (*i.e.* F1 and F2) and late (*i.e.* F3 and F4) stage fibrotic liver tissues, respectively, under the guidance of data reported in the literature (see Table 1). Although the same volume fraction was chosen for F1 and F2 (or F3 and F4), spatial characteristics of those inclusions were different in numerical models as shown in Figure 3.

The grid spacing within the entire computing domain was uniform and the pixel/grid size was 0.1-mm $\times$ 0.1-mm. Mesh sensitivity tests were performed to verify that results were not sensitive to the chosen grid size. Compression and SW velocity parameters (*i.e.* compressional sound speed, shear wave speed, and mass density) were assigned to each and every pixel in the rectilinear [computing] grid. In addition to material properties presented in subsection D of the Materials and Methods Section above, other key simulation details can be found in Table 2. One cycle of low-frequency (*i.e.* 50Hz, 100Hz, and 150Hz) transient (up–down) vibration (see the green vertical line in Figure 4) was prescribed to generate SW that propagates laterally (see the arrow in Figure 4) for each realization. The particle motion (also known as the SW polarization direction) followed the up–down direction (Figure 4) and was perpendicular to the SW propagation direction. The simulation duration was approximately 0.01 second to allow the induced SW to propagate through the entire ROI. Details and a brief justification of this computing domain model including boundary conditions can be found in Appendix B.

F. Assessment of SWS Distributions

To reduce memory usage in the calculations, only 49×48 ($n \times q$) time-resolved SWS curves obtained within the ROI (see Figure 4) were stored. In other words, we only stored simulated SW data from a coarsened uniform rectilinear grid whose grid spacing was 0.4×0.4 -mm, as shown in Figure 5. The SWS at an arbitrary location (m, p) will be estimated by detecting the time-delay (τ) between two time-resolved particle velocity curves located at (m, p) and (l, p), respectively, using a correlation-based method (Palmeri *et al.*, 2008). This process resulted in 2256 (48×47) SWS values for each simulated field. More specifically, SWS values were estimated at different width positions (*i.e.* row positions in the left plot of Figure 5) for each depth (*i.e.* column positions in the left plot of Figure 5). In this study, the d was fixed at 0.4 mm and the time-delay τ was evaluated between two (horizontally) adjacent points, as shown in Figure 5. Then, a 2D map of SWS values in the field of view can be obtained. PDF parameters were estimated by fitting simulated SWS data to respective equations (see Eqn. (6) - (9)). Only SWS data ranged from 5% to 95% quantiles were used.

In addition to analyses of all 11,000 SWS data together (see Table 2), we also randomly selected 100 data points from all 11,000 data points in order to mimic “clinical” SWS data. This process was repeated 100 times to generate 100 realizations of simulated “clinical” SWS data for each fibrosis stage.

Results

When histograms obtained from all 11,000 data points were examined, we found that the overall distribution was unsymmetrical as shown in Figure 6. The skewness (Bowker and Lieberman, 1972) was calculated. We found that fairly consistent skewness values were obtained. In all six cases, the skewness was positive, denoting the SWS data were skewed toward the right. Of note, the skewness of any perfectly symmetric distribution (*e.g.* Gaussian distribution) is zero.

Representative simulated ‘clinical’ SWS data (*i.e.* 100 data points) are displayed in Figure 7 as histograms. Relative AIC and BIC values were calculated from those simulated ‘clinical’ SWS data and their results were listed in Table 3. Relative AIC and BIC values were obtained by normalizing absolute AIC or BIC values (see Eqns. 10-11) obtained from other three PDF models by the respective AIC or BIC value from the derived PDF. Data in Table 3 indicated that the overall performance of the derived PDF performed is better than other three PDFs, though the relative differences of AIC and BIC among these four PDFs were small ($< 3\%$). Results shown in Table 3 were consistent with the visual perception shown in Figure 7.

Using simulated “clinical” SWS data, parameters estimated by the derived PDF, GAD and LND were converted to means and standard deviations of the underlying shear modulus values. Comparative results are shown in Table 4. When the excitation frequency was 50 Hz, all four PDFs essentially gave the similar mean values of the fitted shear moduli. When the excitation frequency increased to 150 Hz, the discrepancies becomes more noticeable. Particularly, at the 150 Hz and with 30% inclusions, mean values between the proposed PDF and the GAD differed by approximately 24%. The difference between the proposed PDF and

the LND increased to roughly 46% under the same condition. Results in Table 4 also suggested that standard deviations estimated using the proposed PDF were considerably lower than those obtained by GAD and LND for all cases investigated.

We also found that, overall, the fluctuation of SWS decreased in all heterogeneous media as the traveling distance increased. In order to demonstrate that, we replot SWS values obtained from the excitation frequency of 150 Hz along the SW propagation direction in Figure 8 below as an example. Results shown in Figure 8b and 8c were SWS measurements averaged from 48 (lateral) lines (see the dashed lines in Figure 8a).

These results in Figure 8 suggest that the SWS became stable (low variance and convergence to the mean SWS) after the SW travels a short distance. In the wave physics literature, the term “short” often referred to the fact the distances are on the same order as respective wavelengths. We assumed that the stabilization is achieved once the absolute difference between the instantaneous mean SWS (over multiple realizations) along SW propagation direction and the mean SWS through fitting the proposed PDF is less than 0.1 m/s. The traveling distance by which the wave stabilization is achieved is defined as the stabilization distance. As shown in Figure 9, the required stabilization distance increased from 8 mm to 14 mm with the increase of heterogeneity from 10% of inclusions to 30% of inclusions. Also, the stabilization distance is not correlated to the excitation frequency, as shown in Figure 9 below.

Discussion

One contribution of this work is that we found that the simulated SWS values in heterogeneous media have un-symmetric distributions (see Figure 6). At the same time, through the principle of ME, the derived PDF (see Eqn. (6)) has an asymmetric form. Overall, the proposed PDF performed the best among all four PDFs (see Tables 3 and 4). It is also worth noting that the performance of GGD was actually close to that of the derived PDF. However, GGD has a complex form (*i.e.* Gamma function and three parameters; see in Eqn. (9)) and two parameters of GGD have no physical meanings. Consequently, the proposed PDF is advantageous in terms of both its solid theoretical basis and physically meaningful parameters. Certainly, this observation needs to be further investigated using *in vivo* biological data.

We also noticed that none of four PDFs fitted the right tails of simulated SWS data (*e.g.* Figure 2 or 7) well. High SWS estimates at the right tails were largely due to strong local wave interference patterns in heterogeneous tissues. In the future, we will use heavy-tailed distributions such as Weibull and Burr (Type XII) distributions (Embrechts *et al.*, 1997) to fit the simulated SWS data (see Figure 7) and compare their performance to the proposed PDF.

Results in Table 4 also indicated that different mean values of shear moduli, as well as different standard deviations, were obtained when different PDFs were used to fit the same data. The difference in terms of the mean shear modulus could be as high as 24% between the derived PDF and the Gaussian for the models that contain 30% inclusions and were excited by 150 Hz perturbations. It was also found that such discrepancies increased as the

percentage of fibrosis increased from 10% to 30%, as shown in Table 4. This observation may have potential clinical implications. Because better thresholds/cut-off values can perhaps be determined for staging liver fibrosis if a better statistical PDF model can be adopted. As of now, the Gaussian Distribution PDF has been implicitly used (Sporea *et al.*, 2014; Verlinden *et al.*, 2016). Moreover, two parameters (*i.e.* G_E and G_D) of the derived PDF are the mean and variance of the underlying shear modulus of the stochastic medium. Certainly, more work is needed in order to demonstrate the proposed PDF is indeed advantageous.

The stochastic liver tissue model consisted of two components: normal liver tissues and (micro-packet of) fibrotic liver tissues. In the literature, normal liver shear modulus was measured to be 3.7-7.0 kPa in men and 3.3-6.8 kPa in women, respectively (Kim *et al.*, 2012). In this study, the normal liver shear modulus was set to be around 4 kPa (SWS: 1.8 m/s) and the shear modulus value of fibrotic liver tissues was elevated to 400 kPa (SWS: 20 m/s). Because, to our knowledge, there is no mechanical testing data available for fibrotic (collagenous) liver tissues at the spatial scale of 100 micrometers, the (micro-packet) of fibrotic tissues was chosen to be close to the shear modulus values of arterial tissues (Khamdaeng *et al.*, 2012). We have varied the shear modulus values of the fibrotic tissues from 900 kPa (SWS: 30 m/s) to 2.5 MPa (SWS: 50 m/s) and findings were not sensitive to the choice of the shear modulus values of the fibrotic tissues.

To obtain the M-C simulated SWS distribution, pointwise estimations of SWS were performed for each realization. The processing kernel length was 0.4 mm. To verify the kernel length sensitivity for the simulated SWS distribution, our results were reprocessed using a processing kernel length of 1.2 mm. We found that the means of SWS remained to be the same but the variances of SWS were typically reduced by approximately 5%.

Our results shown in Figures 8 and 9 also suggested that wave fronts with a plane wave propagating in a lossless (elastic) medium may be stabilized after certain stabilization distances, dependent on the nature of the heterogeneous random media. It is easy to see that the presence of inclusions led to some distortions of wave fronts and this phenomenon is known as elastic shear wave scattering. In this study, elastic wave scattering is responsible for variations among estimated local SWS values. The degree of wave distortion was likely proportional to how heavily inclusions were presented along the wave propagation pathway. That was why variations in SWS were greater in more heterogeneous media (e.g Figure 8a vs. 8b). Furthermore, such wave distortions due to multiple (elastic) wave scattering were “averaged” along the wave propagation direction and eventually minimized. This finding is consistent with a proof in the literature of applied mathematics (Lewicki, 1994).

Since the derivation of the PDF ignored the viscosity of soft tissue (Yi Zheng, 2013). Thus, the derived PDF is only theoretically valid when the SW propagates within lossless (elastic) media. In other words, the frequency-dependent wave dispersions were ignored in the current derivations. In the future work, we will consider the distribution of phase velocity given heterogeneities in shear modulus and viscosity values. Furthermore, in viscoelastic biological tissues, the shear wave may attenuate quickly before reaching the stabilization distance (approximately 8 – 14 mm). Thus, the validity of our findings in Figures 8 and 9

will be verified in biological tissues in the future. If verified in biological tissues, this observation may help us to determine optimal locations from which the SWS should be tracked by balancing the stabilization of wave fronts and attenuation of SW amplitudes. Furthermore, the stabilization distance was not proportional to the excitation frequency (Figure. 9). We stipulate that this observation is reasonable because the elastic wave scattering is within the Rayleigh Regime, given the wavelength (shear wave frequency: 50Hz, 100Hz, and 150Hz). It is worth noting that estimated mean values of SWS (Table 4) under three excitation frequencies slightly differed (approximately 2-4%), largely due to elastic wave scattering.

It is worth noting that 100 data points were selected to balance the need of approximating the number of data points collected from a single patient in a clinical setting and stability of curving fitting using Eqns. (6)-(9). We verified that the relative difference of the estimated parameters using AIC, BIC were within 2%, when we varied the number of data points from 100 to 200. If the size of data points was reduced to 50, the estimated parameters would differ about 10% as compared to those using 100 data points. In a clinical setting, the number of available SWS measurements is typically 10 – 20 (Cassinotto *et al.*, 2014). Consequently, in order to use the proposed PDF or other PDFs, more SWS measurements may have to be performed on patients. Requiring more measurements could negatively impact the clinical workflow for transient elastography or point shear wave elastography (Shiina *et al.*, 2015). However, if the supersonic shear imaging (Shiina *et al.*, 2015) is used, it is possible that 10-20 independent measurements can be obtained from a single SWS image. Thus, the clinical workloads may not be significantly impacted.

In a similar note, the grid size of the computing domain (see Figure 4) was set to 0.1 mm. This choice was a balance of tradeoffs between the computational cost and the modeling realism. If the grid size would be further reduced the computational cost (mainly memory requirements and computational time) would increase exponentially. If a too large value of the grid size would have been chosen, the computer model may not be able to represent architectural changes at the tissue level (see Figure 3).

There are limitations of the current study. First, in this preliminary study, we used a 2D tissue model along with 2D SW simulations to verify the proposed PDF, which is not limited to 2D based on the derivation (see Appendix B). In 2D SW simulations, complicated wave propagation phenomena such as mode conversion and wave splitting in heterogeneous and perhaps locally anisotropic media cannot be realistically mimicked. Of note, 2D SW simulations have been selected because computational demands of 3D SW simulations in K-Wave are prohibitively high given our computational resources. Second, as explained before in the Section Materials and Methods, the current setting of SW simulations is close to TE or Magnetic Resonance Imaging-based SWE. Acoustic radiation force-induced SWE has more complex SW wave fronts. The applicability of the proposed PDF needs to be verified. In the future, 3D M-C simulations of acoustic radiation force-induced SWE will be repeated for further verifications. We are in the process of extending an advanced ultrasound simulation platform (Wang *et al.*, 2015) for SWE simulations. Third, also due to the limitation of computational resources, we selected a small computing domain (an approximately 90 mm × 22 mm) containing a 20 mm × 20 mm ROI. The dimension perpendicular to the SW

propagation direction is on the order of SW wavelength investigated. Because of the periodic boundary (see Appendix B), this setting is different than SW waveguides. In SW waveguides, the outward SW motion is often highly constrained. We also varied the size of the ROI to investigate whether or not the SWS is sensitive to the size of the ROI (see Figure 4). Under the same conditions, outcomes between three different domain sizes (*i.e.* 10 mm $\times$ 10 mm, 20 mm $\times$ 20 mm and 30 mm $\times$ 30 mm) differed within 5%. Some small differences are expected given the nature of M-C simulations.

In this work, we describe options chosen and provide justifications for our choices. Overall, the study design is appropriate for the first feasibility study, despite aforementioned limitations. Future work includes 3D SW simulations with a 3D stochastic tissue model and applications of the proposed PDF to biological data.

Conclusion

In summary, a PDF of the SWS distribution in multi-phase stochastic media was derived by the principle of ME. Given preliminary results presented in this study, this derived PDF can perform well for fitting SWS measurements data. Also, the parameters involved in the derived PDF can be related to the mechanical properties of the medium being imaged. This new method does seem to add value and could represent a feasible path to the study uncertainties in SWE due to tissue heterogeneity. This initial feasibility study is encouraging and we believe that the method warrants further studies.

Acknowledgments

This study was partially supported by a research grant from the US National Institutes of Health (R15CA179409). The computing time for K-WAVE simulations was provided by a grant from Michigan Tech's Superior HPC cluster. Dr. Gowtham provided technical support for the use of Superior. We also thank our colleagues Prof. Sean Kirkpatrick and Dr. Bo Peng (Michigan Tech University) for fruitful discussions.

Appendix A — Derivation of PDF for SWS Distribution in Random Multiphase Media

Let's consider an elastic heterogeneous medium, which consists of multiple isotropic phases with elastic bulk modulus (K_i), shear modulus (G_i), mass density (ρ_i), and the volume concentration (c_i , $\sum c_i = 1$), respectively. The subscript i denotes those phase indices, respectively. For simplicity, the multi-phase medium is treated as effectively isotropic and macroscopically homogeneous, which is characterized by effective bulk modulus (K), effective shear modulus (G) and effective density (ρ , $\rho = \sum \rho_i c_i$) (Beltzer and Sato, 2003). Without the loss of generality, a set of physical properties $J = (K_i, G_i, \rho_i, c_i)$ is defined for this random multi-phase medium. In this derivation, both K and G are random variables.

The macroscopic SWS (V_s) of this elastic random medium can be related to the effective shear modulus G by (Wells and Liang, 2011),

$$V_s = \sqrt{\frac{G}{\rho}} \quad (\text{A1})$$

where ρ is effective density.

Recall that both G and V_s are random variables. We define $F(V_s)$ as a cumulative distribution function (CDF) of V_s . By definition, $F(V_s)$ can be written as follows (Ogunnaike, 2009),

$$F(V_s) = F\{v \geq V_s\} = F\left\{\sqrt{\frac{G}{\rho}} \geq V_s\right\} = F\{G \geq \rho \cdot V_s^2\} = \int_0^{\rho \cdot V_s^2} p(G) dG \quad (\text{A2})$$

where $p(G)$ is the probability density function (PDF) of effective shear modulus G . Hence, the PDF of V_s can be written as,

$$p(V_s) = \frac{\partial F(V_s)}{\partial V_s} = \frac{\partial \int_0^{\rho \cdot V_s^2} p(G) dG}{\partial V_s} = p(\rho \cdot V_s^2) \cdot 2\rho V_s \quad (\text{A3})$$

Now we can establish a link between $p(V_s)$ and $p(G)$ as follows,

$$p(V_s) = p(G) 2V_s \rho \quad (\text{A4})$$

The Jaynes' principle of maximum entropy states that the information entropy (H) is given by (Jaynes, 1957b),

$$H = - \int_{-\infty}^{+\infty} p(G) \ln \frac{p(G)}{m(G)} dG \quad (\text{A5})$$

where $m(G)$ is an initial distribution of data and is typically assigned according to a *prior* understanding of data G . The Jaynes' entropy H can reach maximum if $p(G)$ can reflect the data distribution in the best possible way. Consequently, maximization of H leads to an optimized $p(G)$ that best describes the given data G .

$m(G)$ was assigned to be a uniform distribution in the current study so that no bias was injected. Consequently, Eqn. (A5) is equivalent to the classical Shannon's entropy given by

$$H = - \int_{-\infty}^{+\infty} p(G) \ln p(G) dG \quad (\text{A6})$$

Now we maximize H that are subjected to three constraints, *i.e.* the zeroth, first and second order moments as follows,

$$\int_{-\infty}^{+\infty} p(G) dG = 1 \quad (\text{A7-a})$$

$$\int_{-\infty}^{+\infty} p(G) G dG = G_E \quad (\text{A7-b})$$

$$\int_{-\infty}^{+\infty} p(G) (G - G_E)^2 dG = G_D \quad (\text{A7-c})$$

To maximize H , the class Lagrange Multiplier method (Bertsekas, 1995) was used and the Lagrange function was constructed as follows,

$$L(p, \lambda) = - \int_{-\infty}^{+\infty} p(G) \ln p(G) dG + \lambda_0 \left(\int_{-\infty}^{+\infty} p(G) dG - 1 \right) + \lambda_1 \left(\int_{-\infty}^{+\infty} p(G) G dG - G_E \right) + \lambda_2 \left(\int_{-\infty}^{+\infty} p(G) (G - G_E)^2 dG - G_D \right) \quad (\text{A8})$$

where λ_0 , λ_1 and λ_2 are Lagrange multipliers.

$L(p, \lambda)$ reaches the maximum when $\frac{\partial L(p, \lambda)}{\partial p(G)} = 0$. The derivative of $L(p, \lambda)$ with respect to $p(G)$ can be expressed as (MacKay, 2003; Cover and Thomas, 1991),

$$\frac{\partial L(p, \lambda)}{\partial p(G)} = - \ln p(G) + \lambda_0 + \lambda_1 + \lambda_2 (G - G_E)^2 \quad (\text{A9})$$

Solving Eqn. (A9), we have

$$p(G) = e^{\lambda_0 + \lambda_1 G + \lambda_2 (G - G_E)^2} \quad (\text{A10})$$

Substituting Eqn. (A10) into Eqn. (A7-a), we obtain following equations

$$\int_{-\infty}^{+\infty} e^{\lambda_0 + \lambda_1 G + \lambda_2 (G - G_E)^2} dG = 1 \quad (\text{A11-a})$$

which provides

$$e^{\lambda_0} \sqrt{\frac{\pi}{-\lambda_2}} \int_{-\infty}^{+\infty} e^{\lambda_1 G} f(G) dG = 1 \quad (\text{A11-b})$$

where $f(G)$ is the Gaussian distribution with mean G_E and variance σ^2 with $\sigma = \sqrt{\frac{-1}{2\lambda_2}}$

According to the moment-generating function of a Gaussian random variable, Eqn. (A11-b) can be rewritten as follows,

$$e^{\lambda_0} \sqrt{\frac{\pi}{-\lambda_2}} e^{G_E \lambda_1 + \frac{\sigma^2 \lambda_1^2}{2}} = 1 \quad (\text{A12})$$

Similarly, replacing $p(G)$ in Eqn. (A7-b) with Eqn. (A10), we can also obtain following equation

$$\int_{-\infty}^{+\infty} e^{\lambda_0 + \lambda_1 G + \lambda_2 (G - G_E)^2} G dG = G_E \quad (\text{A13-a})$$

Some algebra shows that Eqn. (A13-a) becomes

$$e^{\lambda_0 + \lambda_1 G_E^2 - \lambda_2 \left(G_E - \frac{\lambda_1}{2\lambda_2}\right)^2} \sqrt{2\pi\sigma} E(G) = G_E \quad (\text{A13-b})$$

where $E(G) = G_E - \frac{\lambda_1}{2\lambda_2}$. By using Eqn. (A13-b) over Eqn. (A12), we can obtain

$$\frac{e^{\lambda_0 + \lambda_1 G_E^2 - \lambda_2 \left(G_E - \frac{\lambda_1}{2\lambda_2}\right)^2} \sqrt{2\pi\sigma} E(G)}{e^{\lambda_0} \sqrt{\frac{\pi}{-\lambda_2}} e^{G_E \lambda_1 + \frac{\sigma^2 \lambda_1^2}{2}}} = \frac{G_E}{1} \quad (\text{A14-a})$$

By simplifying Eqn. (A14-a), we obtain

$$G_E - \frac{\lambda_1}{2\lambda_2} = G_E, \text{ which gives}$$

$$\lambda_1 = 0 \quad (\text{A14-b})$$

By plugging $\lambda_1 = 0$ into Eqn. (A11-b), we obtain $\lambda_0 = \ln \sqrt{\frac{\lambda_1}{-\pi}}$.

Replacing $p(G)$ in Eqn. (A7-c) with Eqn. (A10), we obtain following equations,

$$e^{\lambda_0} \int_{-\infty}^{+\infty} \omega^2 e^{\lambda_2 \omega^2} d\omega = G_D, \omega = G - G_E \quad (\text{A15-a})$$

$$\text{which shows that } \lambda_2 = \frac{-1}{2G_D}$$

Thus, Eqn. (A10) becomes a form of the Gaussian distribution given by

$$p(G) = \frac{1}{\sqrt{2\pi G_D}} e^{-\frac{(G-G_E)^2}{2G_D}} \quad (\text{A16})$$

$$\text{where } \lambda_0 = \ln \frac{1}{\sqrt{2\pi G_D}}, \lambda_1 = 0, \text{ and } \lambda_2 = \frac{-1}{2G_D}.$$

Now, we can substitute Eqn. (A1) and (A13) into Eqn. (A4). The final form of the PDF of the SWS $p(V_s)$ is given as follows,

$$p(V_s) = \frac{1}{\sqrt{2\pi G_D}} e^{-\frac{(V_s^2 \rho - G_E)^2}{2G_D}} 2\rho V_s \quad (\text{A17})$$

Appendix B — A Brief Description of K-Wave Simulations

The elastic shear wave propagation was simulated using an open-source wave simulator K-Wave (Bradley E. Treeby, 2014). In a simple form, the elastic wave propagation in an isotropic linearly elastic medium is governed by two coupled first-order partial differential equations (PDEs) (Bradley E. Treeby, 2014):

$$\frac{\partial \sigma_{ij}}{\partial t} = \lambda \delta_{ij} \frac{\partial v_k}{\partial x_k} + \mu \left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right) \quad (\text{B1})$$

$$\frac{\partial v_i}{\partial t} = \frac{1}{\rho_0} \frac{\partial \sigma_{ij}}{\partial x_i} \quad (\text{B2})$$

where v , x , σ , t and ρ_0 , δ_{ij} are the particle velocity, the coordinate system, stress tensor, time, mass density and Kronecker delta, respectively. In Eqn. (B1), λ and μ are the Lamé parameters. All subscripts follow Einstein notation in this Appendix.

In this study, Eqns. (B1-B2) were numerically solved by Fourier pseudo-spectral method (Liu, 1999; Caputo *et al.*, 2011) in K-WAVE on a 2D rectilinear grid $[0, L_x] \times [0, L_y]$. A graphical illustration of the computing domain is given in Figure B1. A transient elastography-like excitation was applied onto a vertical line $x_1 = L_{xe}$ (see Figure B1) as an interior boundary condition,

$$\sigma_2(L_{xe}, x_2, t) = \begin{cases} k \sin 2\pi f t, & 0 \leq x_2 \leq L_y, \quad 0 \leq t \leq \frac{1}{f} \\ 0, & 0 \leq x_2 \leq L_y, \quad t \geq \frac{1}{f} \end{cases} \quad (\text{B3})$$

where f is the excitation frequency, k is an arbitrary constant and t is the time. Basically, this interior boundary states that one cycle of a perturbation (σ_2) is prescribed near the ROI to induce plane shear wave propagating along the x_1 direction.

The well-known Dirichlet periodic boundary condition was applied onto four exterior edges (see Lines 1-4 in Figure B1) to create a “mirroring” structure around all four edges. Loosely speaking, under this periodic boundary condition, the SW wave-front can re-appear at Line 4 when the SW wave-front passed Line 2. Mathematically, this exterior periodic boundary condition can be written as follows:

$$\sigma_{ij}(0, x_2, t) = \sigma_{ij}(L_x, x_2, t), \quad 0 \leq x_2 \leq L_y \quad (\text{B4})$$

$$\sigma_{ij}(x_2, 0, t) = \sigma_{ij}(x_2, L_y, t), \quad 0 \leq x_2 \leq L_x \quad (\text{B5})$$

$$v_i(0, x_2, t) = v_i(L_x, x_2, t), \quad 0 \leq x_2 \leq L_y \quad (\text{B6})$$

$$v_i(x_1, 0, t) = v_i(x_1, L_y, t), 0 \leq x_1 \leq L_x \quad (\text{B7})$$

In this study, the above-mentioned periodic boundary condition was used, as opposed to the perfectly matched layer (PML) for two reasons. First, the PML boundary condition resulted in apparent constraints (*i.e.* absorption) around the top and bottom boundaries (particularly, Lines 1 and 3 in Figure B1). That would be a violation of the plane shear wave assumption. Second, the absorption of the PML in K-WAVE was mainly designed for high-frequency compression waves (in MHz) and therefore, was not well fitted for low-frequency (50-200 Hz) SW in terms of its effect of wave absorption.

Figure B1.

A graphical illustration of the boundary conditions defined for K-Wave plane SW simulation presented in the Materials and Methods Section. The computing area is defined on a rectilinear grid $[0, L_x] \times [0, L_y]$. The green arrow indicates the SW propagation direction.

References

- Akaike H. Information theory and an extension of the maximum likelihood principle. 2nd International Symposium on Information Theory. 1973
- Treeby B, C B, Jaros J. K-Wave User Manual. 2012
- Bamber J, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, Cantisani V, Correias JM, D'Onofrio M, Drakonaki EE, Fink M, Friedrich-Rust M, Gilja OH, Havre RF, Jenssen C, Klauser AS, Ohlinger R, Saftoiu A, Schaefer F, Sporea I, Piscaglia F. EFSUMB Guidelines and Recommendations on the Clinical Use of Ultrasound Elastography. Part 1: Basic Principles and Technology. *Ultraschall in Der Medizin*. 2013; 34:169–84. [PubMed: 23558397]
- Barr RG, Ferraioli G, Palmeri ML, Goodman ZD, Garcia-Tsao G, Rubin J, Garra B, Myers RP, Wilson SR, Rubens D, Levine D. Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement. *Radiology*. 2015; 276:845–61. [PubMed: 26079489]
- Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology*. 1996; 24:289–93. [PubMed: 8690394]
- Beltzer AI, Sato T. Probability distribution of wave velocity in heterogeneous media due to random phase configuration. *Wave Motion*. 2003; 38:221–7.
- Bercoff J, Tanter M, Fink M. Supersonic shear imaging: a new technique for soft tissue elasticity mapping. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2004; 51:396–409. [PubMed: 15139541]
- Bertsekas, DP. Nonlinear programming. Belmont, Mass: Athena Scientific; 1995.
- Birbrair A, Zhang T, Files DC, Mannava S, Smith T, Wang ZM, Messi ML, Mintz A, Delbono O. Type-1 pericytes accumulate after tissue injury and produce collagen in an organ-dependent manner. *Stem Cell Res Ther*. 2014; 5

- Bowker, AH., Lieberman, GJ. Engineering statistics. Englewood Cliffs, N.J.: Prentice-Hall; 1972.
- Bradley E, Treeby JJ, Rohrbach Daniel, Cox BT. Modelling Elastic Wave Propagation Using the k-Wave MATLAB Toolbox. IEEE International Ultrasonics Symposium Proceedings. 2014
- Caputo M, Carcione JM, Cavallini F. Wave simulation in biologic media based on the Kelvin-Voigt fractional-derivative stress-strain relation. *Ultrasound Med Biol*. 2011; 37:996–1004. [PubMed: 21601139]
- Carey E, Carey WD. Noninvasive tests for liver disease, fibrosis, and cirrhosis: Is liver biopsy obsolete? *Cleveland Clinic journal of medicine*. 2010; 77:519–27. [PubMed: 20682514]
- Casella, G., Berger, RL. Statistical inference. Pacific Grove, Calif: Brooks/Cole Pub. Co.; 1990.
- Cassinotto C, Lapuyade B, Mouries A, Hiriart JB, Vergniol J, Gaye D, Castain C, Le Bail B, Chermak F, Foucher J, Laurent F, Montaudon M, De Ledinghen V. Non-invasive assessment of liver fibrosis with impulse elastography: comparison of Supersonic Shear Imaging with ARFI and FibroScan(R). *J Hepatol*. 2014; 61:550–7. [PubMed: 24815876]
- Castera LFJ, Bernard PH, Carvalho F, Allaix D, Merrouche W, Couzigou P, de Ledinghen V. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology*. 2010; 51:828–35. [PubMed: 20063276]
- Castera L, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, Couzigou P, de Ledinghen V. Pitfalls of Liver Stiffness Measurement: A 5-Year Prospective Study of 13,369 Examinations. *Hepatology*. 2010; 51:828–35. [PubMed: 20063276]
- Cover, TM., Thomas, JA. Elements of information theory. New York: Wiley; 1991.
- de Ledinghen V, Wong VW, Vergniol J, Wong GL, Foucher J, Chu SH, Le Bail B, Choi PC, Chermak F, Yiu KK, Merrouche W, Chan HL. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan(R). *J Hepatol*. 2012; 56:833–9. [PubMed: 22173167]
- Deffieux T, Gennisson JL, Bercoff J, Tanter M. On the Effects of Reflected Waves in Transient Shear Wave Elastography. *Ieee T Ultrason Ferr*. 2011; 58:2032–5.
- Deffieux T, Gennisson JL, Larrat B, Fink M, Tanter M. The Variance of Quantitative Estimates in Shear Wave Imaging: Theory and Experiments. *Ieee Transactions on Ultrasonics Ferroelectrics and Frequency Control*. 2012; 59:2390–410.
- Doherty JR, Trahey GE, Nightingale KR, Palmeri ML. Acoustic radiation force elasticity imaging in diagnostic ultrasound. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2013; 60:685–701. [PubMed: 23549529]
- Duck, FA. Physical properties of tissue : a comprehensive reference book. CA, USA: Academic Press: San Diego; 990.
- Embrechts, P., Klüppelberg, C., Mikosch, T. Modelling extremal events for insurance and finance. New York: Springer; 1997.
- Ferraioli G, Filice C, Castera L, Choi BI, Sporea I, Wilson SR, Cosgrove D, Dietrich CF, Amy D, Bamber JC, Barr R, Chou YH, Ding H, Farrokh A, Friedrich-Rust M, Hall TJ, Nakashima K, Nightingale KR, Palmeri ML, Schafer F, Shiina T, Suzuki S, Kudo M. Wfumb Guidelines and Recommendations for Clinical Use of Ultrasound Elastography: Part 3: Liver. *Ultrasound Med Biol*. 2015; 41:1161–79. [PubMed: 25800942]
- Ferraioli G, Parekh P, Levitov AB, Filice C. Shear wave elastography for evaluation of liver fibrosis. *J Ultrasound Med*. 2014; 33:197–203. [PubMed: 24449721]
- Findley DF. Counterexamples to Parsimony and Bic. *Annals of the Institute of Statistical Mathematics*. 1991; 43:505–14.
- Friedrich-Rust M, Rosenberg W, Parkes J, Herrmann E, Zeuzem S, Sarrazin C. Comparison of ELF, FibroTest and FibroScan for the non-invasive assessment of liver fibrosis. *BMC Gastroenterol*. 2010; 10:103. [PubMed: 20828377]
- Goldschmidt I, Streckenbach C, Dingemann C, Pfister ED, di Nanni A, Zapf A, Baumann U. Application and limitations of transient liver elastography in children. *J Pediatr Gastroenterol Nutr*. 2013; 57:109–13. [PubMed: 23539048]
- Huang Y, de Boer WB, Adams LA, MacQuillan G, Rossi E, Rigby P, Raftopoulos SC, Bulsara M, Jeffrey GP. Image analysis of liver collagen using sirius red is more accurate and correlates better

- with serum fibrosis markers than trichrome. *Liver International*. 2013; 33:1249–56. [PubMed: 23617278]
- Jaynes ET. Information theory and statistical mechanics. *Phys Rev*. 1957a; 108:171–97.
- Jaynes ET. Information theory and statistical mechanics. *Phys Rev*. 1957b; 106:620–30.
- Khamdaeng T, Luo J, Vappou J, Terdtoon P, Konofagou EE. Arterial stiffness identification of the human carotid artery using the stress-strain relationship in vivo. *Ultrasonics*. 2012; 52:402–11. [PubMed: 22030473]
- Kim BK, Kim SU, Choi GH, Han WK, Park MS, Kim EH, Park JY, Kim DY, Choi JS, Yang SC, Choi EH, Song K, Ahn SH, Han KH, Chon CY. “Normal” liver stiffness values differ between men and women: A prospective study for healthy living liver and kidney donors in a native Korean population. *Journal of Gastroenterology and Hepatology*. 2012; 27:781–8. [PubMed: 22098121]
- Lewicki P. Long Time Evolution of Wavefronts in Random Media. *SIAM Journal on Applied Mathematics*. 1994; 54
- Liu QH. Large-scale simulations of electromagnetic and acoustic measurements using the pseudospectral time-domain (PSTD) algorithm. *Ieee Transactions on Geoscience and Remote Sensing*. 1999; 37:917–26.
- MacKay, DJC. Information theory, inference, and learning algorithms. Cambridge, UK; New York: Cambridge University Press; 2003.
- Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, Sterling RK, Shiffman ML, Stravitz RT, Sanyal AJ. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology*. 2003; 37:1286–92. [PubMed: 12774006]
- Nightingale K, McAleavey S, Trahey G. Shear-wave generation using acoustic radiation force: in vivo and ex vivo results. *Ultrasound Med Biol*. 2003; 29:1715–23. [PubMed: 14698339]
- Ogunnaike, BA. Random Phenomena: Fundamentals of Probability and Statistics for Engineers. CRC Press; Taylor & Francis: 2009.
- Palmeri ML, Wang MH, Dahl JJ, Frinkley KD, Nightingale KR. Quantifying hepatic shear modulus in vivo using acoustic radiation force. *Ultrasound in Medicine and Biology*. 2008; 34:546–58. [PubMed: 18222031]
- Parkes J, Guha IN, Roderick P, Rosenberg W. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. *J Hepatol*. 2006; 44:462–74. [PubMed: 16427156]
- Ryaben'kii, VS., Tsynekov, S. A theoretical introduction to numerical analysis. Boca Raton, FL: Chapman & Hall/CRC; 2007.
- Robbins, SL., Kumar, V., Cotran, RS. Robbins and Cotran pathologic basis of disease. Philadelphia, PA: Saunders/Elsevier; 2010.
- Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. *Hepatology*. 2006; 43:S113–20. [PubMed: 16447288]
- Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, Christidis C, Zioli M, Poulet B, Kazemi F, Beaugrand M, Palau R. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol*. 2003; 29:1705–13. [PubMed: 14698338]
- Sarvazyan AP, Rudenko OV, Swanson SD, Fowlkes JB, Emelianov SY. Shear wave elasticity imaging: a new ultrasonic technology of medical diagnostics. *Ultrasound Med Biol*. 1998; 24:1419–35. [PubMed: 10385964]
- Seeram Ramakrishna, ZMH., Ganesh, V Kumar, Andrew, W Batchelor, Joerg, Mayer. An Introduction to Biocomposites. Imperial College Press; 2004.
- Shiina T, Nightingale KR, Palmeri ML, Hall TJ, Bamber JC, Barr RG, Castera L, Choi BI, Chou YH, Cosgrove D, Dietrich CF, Ding H, Amy D, Farrokh A, Ferraioli G, Filice C, Friedrich-Rust M, Nakashima K, Schafer F, Sporea I, Suzuki S, Wilson S, Kudo M. Wfumb Guidelines and Recommendations for Clinical Use of Ultrasound Elastography: Part 1: Basic Principles and Terminology. *Ultrasound in Medicine and Biology*. 2015; 41:1126–47. [PubMed: 25805059]
- Sporea I, Bota S, Gradinaru-Ta c u O, Sirli R, Popescu A, Jurchi A. Which are the cut-off values of 2D-Shear Wave Elastography (2D-SWE) liver stiffness measurements predicting different stages of liver fibrosis, considering Transient Elastography (TE) as the reference method? *European Journal of Radiology*. 2014; 83:e118–22. [PubMed: 24380640]

- Standish RA, Cholongitas E, Dhillon A, Burroughs AK, Dhillon AP. An appraisal of the histopathological assessment of liver fibrosis. *Gut*. 2006; 55:569–78. [PubMed: 16531536]
- Stenvall A, Larsson E, Strand S, Jonsson B. A small-scale dosimetry model of the liver tissue. *European Journal of Nuclear Medicine and Molecular Imaging*. 2012; 39:S199–S.
- Timothy, J., Hall, AM., Brian, Garra, Paul, Carson, Mark, Palmeri, Kathy, Nightingale, Ted, Lynch, Abdullah, Alturki, Michael, Andre, Stephane, Audiere, Jeffery, Bamber, Richard, Barr, Jeremy, Bercoff, Jessica, Bercoff, Miguel, Bernal, Javier, Brum, Huan, Wee Chan, Shigao, Chen, Claude, Cohen-Bacrie, Mathieu, Couade, Allison, Daniels, Ryan, DeWall, Jonathan, Dillman, Richard, Ehman, SF, Franchi-Abella, Jeremie, Fromageau, Jean-Luc, Gennisson, Jean, Pierre Henry, Nikolas, Ivancevich, Jan, Kalin, Sarah, Kohn, Jennifer, Kugel, Ken, Lee, NL, Liu, Thanasis, Loupas, Joan, Mazernik, Stephen, McAleavey, Veronique, Miette, Stephen, Metz, BM, Morel, Thomas, Nelson, Eric, Nordberg, Jennifer, Oudry, Monali, Padwal, Ned, Rouze, Anthony, Samir, Laurent, Sandrin, Janet, Schaccitti, Cedric, Schmitt, Vijay, Shamdasani, Pehngfei, Song, Pamela, Switalski, Michael, Wang, Keith, Wear, Hua, Xie, Heng, Zhao. Ultrasonics Symposium (IUS), 2013 IEEE International0 13 (unpublished). 2013. RSNA/QIBA: Shear wave speed as a biomarker for liver fibrosis staging.
- Torquato, S. Random heterogeneous materials : microstructure and macroscopic properties. New York: Springer; 2002.
- Verlinden W, Bourgeois S, Gigase P, Thienpont C, Vonghia L, Vanwolleghem T, Michielsens P, Francque S. Liver Fibrosis Evaluation Using Real-time Shear Wave Elastography in Hepatitis C-Monoinfected and Human Immunodeficiency Virus/Hepatitis C-Coinfected Patients. *J Ultrasound Med*. 2016; 35:1299–308. [PubMed: 27151906]
- Wang Y, Helminen E, Jiang JF. Building a virtual simulation platform for quasistatic breast ultrasound elastography using open source software: A preliminary investigation. *Medical Physics*. 2015; 42:5453–66. [PubMed: 26328994]
- Wells PNT, Liang HD. Medical ultrasound: imaging of soft tissue strain and elasticity. *Journal of the Royal Society Interface*. 2011; 8:1521–49.
- Wieckowska A, Feldstein AE. Diagnosis of nonalcoholic fatty liver disease: invasive versus noninvasive. *Semin Liver Dis*. 2008; 28:386–95. [PubMed: 18956295]
- Yi Zheng XC, Aiping Yao, Haoming Lin, Yuanyuan Shen, Ying Zhu, Minhua Lu, Tianfu Wang, Siping Chen. Shear Wave Propagation in Soft Tissue and Ultrasound Vibrometry, Wave Propagation Theories and Applications. 2013
- Zalata GS, a K. Ishak versus META VIR: Terminology, Convertibility and Correlation with Laboratory Changes in Chronic Hepatitis C. 2011
- Zhao H, Song P, Urban MW, Kinnick RR, Yin M, Greenleaf JF, Chen S. Bias observed in time-of-flight shear wave speed measurements using radiation force of a focused ultrasound beam. *Ultrasound Med Biol*. 2011; 37:1884–92. [PubMed: 21924817]

Figure 1.
A graphic illustration of the presentation structure in the Section of Materials and Methods.

Figure 2.

A workflow involving in the simulation of SW propagation through a stochastic two-phase medium using the K-Wave simulator: (a) a plot showing simulated SW that propagates through the medium downward and, (b) a histogram of estimated SWS values along the SW propagation direction, along with four fitted PDFs.

Figure 3.

Schematic illustrations of the stochastic tissue Model: (a) a 2D illustration of liver anatomy; (b) Stage F1 with 8% collagenous tissue; (c) Stage F2 with 8% collagenous tissue; (d) Stage F3 with 10% collagenous tissues; and (e) Stage F4 with 25% collagenous tissues. In (b)-(e), the red is normal liver tissue and the blue is collagenous connective tissue. Illustrations of fibrosis from F1 to F4 were based on the METAVIR classifications (Bedossa and Poynard, 1996).

Figure 4.

An illustration of computing domain used for all K-Wave simulations. A (20 mm × 20mm) region of interest (ROI) containing either 10% or 30% inclusions was embedded into a large (90 mm × 22 mm) uniform background. The green vertical line indicates the location of initial mechanical vibration, while the green arrow represents the SW propagation direction.

Figure 5.

A schematic illustration of SWS estimation. The horizontal (black) arrow in the left plot represents the SW propagation direction while the double vertical arrows in the left plot indicate the excitation direction. The ROI is the same ROI shown in Figure 4. The time-resolved particle velocity curves were recorded for $n \times q$ locations (black dots in the left plot). Each black dot represents a time-resolved particle velocity curve in this illustration. The process of correlation-based shear wave speed estimation is shown in the right flowchart.

Figure 6. Histogram distributions of all M-C simulated SWS data from two different volume fractions (10% and 30%). Simulation details were summarized in Table 2. Skewness was calculated for each histogram.

Figure 7.

Representative histogram distributions of M-C simulated "clinical" SWS data from two different volume fractions (10% and 30%). Each histogram was generated using 100 data points and simulation details were summarized in Table 2. Four PDFs were overlaid with the histogram on each plot.

Figure 8.

Plots (b and c) of SWS values along shear wave propagation direction (excitation frequency of 150 Hz) based on all simulated SWS data. The horizontal (black) arrow in (a) represents the SW propagation direction while the double (green) vertical arrows in (a) indicate the excitation direction. The green lines in (b) and (c) indicate respective mean values obtained through fitting of the derived PDF.

Figure 9.

Plots of mean values of SWS along the shear wave propagation direction under two different volume fraction of inclusions (*i.e.* 10%, 30%). Each plot illustrates results obtained from three different SW frequencies (50Hz, 100Hz, and 150Hz). The black arrows represent the stabilization distance.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Collagen proportional area (CPA) for 4 different liver fibrosis stages (F1-F4). Data were taken from reference (Huang *et al.*, 2013).

METAVIR stage	F0	F1	F2	F3	F4
CPA	2.2~9.67%	1.8~15.97%	2.26~16.68%	4.96~20.73%	7.8~32.67%

Table 2

Simulation details of the stochastic tissue model using K-Wave. The correlation length was quantified using two-point correlation function (Torquato, 2002).

CPA	Number of Realizations (for each stage)	Stage (<i>correlation length</i>) (unit: mm)	Number of SWS measurements (for each stage)
10%	5	F1 (<i>0.5</i>), F2 (<i>0.6</i>)	11,000
30%	5	F3 (<i>1.1</i>), F4 (<i>1.3</i>)	11,000

Tabulated results about relative AIC and BIC values using 100 realizations of simulated ‘clinical’ data. Relative AIC and BIC values were obtained by normalizing absolute AIC or BIC values obtained from other three pdf models by the respective AIC or BIC value from the derived PDF.

Table 3

Inclusion Volume Fraction	AIC			BIC		
	10%	30%	10%	30%	10%	30%
LND	-0.99	1.01	-0.99	1.01	-0.99	1.01
GGD	-0.99	1.02	-0.99	1.02	-0.99	1.02
GAD	-1	1.01	-1	1.01	-1	1.01
Derived PDF	-1	1	-1	1	-1	1
LND	-0.97	1.02	-0.97	1.02	-0.97	1.02
GGD	-1	1.01	-1	1.01	-1	1.01
GAD	-0.99	1	-0.99	1	-0.99	1
Derived PDF	-1	1	-1	1	-1	1
LND	-0.97	1.03	-0.97	1.03	-0.97	1.03
GGD	-0.99	1.01	-0.99	1.01	-0.99	1.01
GAD	-0.99	1	-0.99	1	-0.99	1
Derived PDF	-1	1	-1	1	-1	1

Table 4

Tabulated means and standard deviations (STD) of underlying shear modulus values using simulated “clinical” SWS data. Those parameters were estimated based on fitted four PDFs: the derived PDF, GAD, LND, and GGD, in two random media containing 10% and 30% inclusions, respectively. Of note, the standard deviation (STD) cannot be directly estimated using GGD (see Eqn. (9)). Data presented in Table 4 were averaged results obtained by fitting 100 data points to respective PDFs in 100 realizations.

		50Hz		100Hz		150Hz	
		Mean (kPa)	STD (kPa)	Mean (kPa)	STD (kPa)	Mean (kPa)	STD (kPa)
10%	Derived PDF	4.13	0.1	4.15	0.09	4.41	0.78
	GAD	4.29	0.35	4.37	0.28	4.70	0.89
	LND	4.27	0.61	5.32	0.56	5.30	1.21
	GGD	4.28	N/A	4.29	N/A	4.84	N/A
30%	Derived PDF	7.88	2.40	8.35	5.54	8.81	6.71
	GAD	7.52	2.44	9.28	5.58	10.93	8.57
	LND	8.13	2.42	11.31	6.73	12.92	8.59
	GGD	7.92	N/A	8.46	N/A	9.01	N/A