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Finite amplitude measurements of the nonlinear parameter B/A for liquid mixtures spanning a range relevant to tissue harmonic mode

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Abstract

The objective of this investigation was to measure the nonlinear parameter B/A using an enhanced finite amplitude distortion technique, based on nonlinear propagation effects analogous to those associated with tissue harmonic imaging. These measurements validate an improved method for measuring the nonlinear parameter B/A , the small-signal speed of sound, and the attenuation coefficient from a single set of ultrasonic measurements. To test the method, measurements were performed on eleven different mixtures of isopropyl alcohol (isopropanol) and water that span the range of concentrations from 0% to 100% isopropanol. Results for B/A ranging from approximately five to eleven were found to be reproducible and in good agreement with previously published values obtained using a thermodynamic method.

Keywords

Nonlinear; Finite Amplitude Method; Nonlinear Parameter B/A ; Attenuation; Sound Speed; Liquid Mixture

BACKGROUND

Among the published methods for measuring the nonlinear parameter B/A in fluids, or fluid-like media such as soft-tissues, there are two primary approaches: thermodynamic methods and finite amplitude methods. Thermodynamic methods are based on measuring the dependence of the small-signal sound velocity on the temperature and static pressure of the host medium. Finite amplitude methods rely on measuring the rate of harmonic distortion with distance for propagation of a finite amplitude wave. Reviews of the experimental methods can be found in a book chapter by Beyer (1998) and an article by Bjørnø (1986). In a review of experimental methods used to determine B/A Beyer (1998) states that, "In all measurements that have been reported by the various methods, accuracies are rarely better than 5%." The thermodynamic methods are typically considered to be more accurate than the finite amplitude methods (Beyer, 1998; Gong *et al.*, 1989; Law *et al.*, 1985). However, application of the finite amplitude technique is pursued here because of the natural relationship between the physics

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of finite amplitude distortion and the physics underpinning harmonic imaging in clinical ultrasonography.

Experimental determination of the nonlinear parameter B/A with the finite amplitude methods is complicated by the diffraction pattern resulting from the bounded nature of the ultrasonic source. Several different approaches have been pursued by researchers at other laboratories to address these complications (Banchet *et al.*, 2000; Banchet and Cheeke, 2000; Dong *et al.*, 1999; Germain *et al.*, 1989; Gong *et al.*, 1984; Law *et al.*, 1985,¹⁹⁸¹; Saito, 1993,1996; Saito *et al.*, 2005; Shklovskaya-Kordi, 1963; Wu and Tong, 1998). Most of these approaches seek to simplify the problem by working in a limited region of the diffracting field, where a plane wave approximation to the beam is applicable.

In one of the earliest papers published on this topic, Shklovskaya-Kordi (1963) measured the finite amplitude distortion of an ultrasonic field in a series of fluids, relative to the distortion in water. The technique employed two planar transducers, placed a fixed distance apart, in a through-transmission watertank experiment. The liquid sample, contained within an acoustically transparent (thin walled) sample chamber, was substituted for a portion of the water path between the transmit and receive transducers. The speed of sound in the liquid sample was assumed to be close to the speed of sound in water, so that the impact of a changing diffraction pattern at the receiving transducer could be ignored. The effects of attenuation within the liquid sample were also ignored. This relative measurement substitution approach is the basis for several subsequently published techniques. This method was later employed by Gong *et al.* 1984 to measure the nonlinear parameter B/A in several fluids of biological interest.

An improvement was made by Gong *et al.* 1989 who added terms to the data reduction model to compensate for an assumed frequency squared attenuation in the fluid sample, and reported the improved measurement of B/A in several biological fluids and tissues. Wu and Tong (1998) used this technique of Gong *et al.* 1989 to report measurements of the nonlinear parameter B/A of mixtures of an ultrasonic contrast agent (Albunex® or Levovist®) and saline. Dong *et al.* 1999 extended the experimental method of Gong *et al.* 1989 and reported measurements of B/A in several tissue-mimicking materials. By working in the far field of a planar piston source, Dong *et al.* 1999 were able to approximate the diffracting field as a plane wave over short propagation distances.

Another method was developed by Law *et al.*, 1985;¹⁹⁸¹ who worked in the extreme near field of a planar transducer and measured the value of B/A in several biological fluids. Working with small distances between the transmitting and receiving transducers permitted these authors to make a plane wave approximation to the beam. They recorded the rate of change in the absolute values of pressure for the fundamental and second harmonic components as a function of distance, along the axis of the transmitted beam. In addition, by extrapolating their measurements back to zero separation distance between the transmitter and receiver, Law *et al.* were able to compensate for any ultrasonic attenuation in the sample medium, without any assumption about the frequency dependence of the attenuation.

The objective of this investigation was to measure the nonlinear parameter B/A , as well as the attenuation and sound speed, of liquid mixtures using a technique that is analogous to that used in tissue harmonic imaging. This was done to validate this approach, which measures all three of these parameters with a single set of ultrasonic measurements. Our approach was to measure these ultrasonic parameters for specific concentrations of isopropyl alcohol (Sigma-Aldrich, 270490) in water and to compare the measured values, obtained with the enhanced method, with previously published values obtained using different techniques (Sehgal *et al.*, 1986).

THEORY

For a weakly nonlinear, monochromatic plane wave propagating in a lossless fluid, the leading order terms of the Fubini solution (Blackstock *et al.*, 1998) accurately describes the evolution of each harmonic component as a function of propagation distance. The amplitude of the second harmonic (2f) component (p_2) starts off zero valued and grows linearly in proportion to the distance traveled, and can be expressed as

$$p_2(x) = \frac{1}{2} \beta \omega x \frac{p_0^2}{\rho_0 c_0^3} \quad (1)$$

where $\beta = 1 + \frac{B}{2A}$ is the coefficient of nonlinearity, intrinsic to the host medium, ω is the angular frequency of the fundamental, x is the propagation distance, p_0 is the initial pressure of the fundamental frequency component of the wave, ρ_0 is the density of the propagation medium, and c_0 is the small-signal sound speed in that medium. Rearranging terms to collect those for pressure and propagation distance on the left hand side, one arrives at a statement of the weakly nonlinear Fubini solution that is applicable to laboratory measurements,

$$\frac{p_2(x)}{x p_0^2} = \frac{\beta \omega}{2 \rho_0 c_0^3} \quad (2)$$

For an experiment in a specified medium, all of the terms in the right hand side of eqn 2 are constants. We would therefore expect the ratio of experimentally measured quantities on the left hand side of eqn 2 to yield the same constant value at each position along the axis of the propagating plane wave. This relationship is equivalent to forms used in experimental studies published by Adler and Hiedemann (1962) and Law *et. al.* (1981). An expression analogous to eqn 2 can be written for the particle velocity of the second harmonic u_2 in terms of the initial particle velocity amplitude u_0 ,

$$\frac{u_2(x)}{x u_0^2} = \frac{\beta \omega}{2 c_0^2} \quad (3)$$

The Fubini solution and its approximations (specifically, eqn 2 and eqn 3) do not incorporate the effects of ultrasonic attenuation. Working with an expression identical to eqn 2 in a medium with non-negligible attenuation, Law *et. al.* 1981 observed that the ratio of the measured values on the left side of eqn 2 decreased exponentially with distance in absorbing media, and noted that extrapolation to zero distance permits the determination of the nonlinearity parameter.

With the proper inclusion of ultrasonic attenuation, the ratio $u_2 / (x u_0^2)$ is no longer a constant that is independent of propagation distance. Accounting for attenuation introduces a decaying exponential term that reduces the signal amplitude with distance traveled, $\exp(-\alpha x)$. In general, the attenuation coefficient $\alpha = \alpha(\omega)$ is a function of frequency and the exponential of decay of the ratio $u_2 / (x u_0^2)$ is a combination of the attenuation at the fundamental and the second harmonic frequencies. Results of a computer simulation showing the ratio $u_2 / (x u_0^2)$ in isopropanol as a function of propagation distance, x , for five different values of attenuation are illustrated in Fig. 1. The horizontal curve is for the case of no attenuation, whereas the other

four curves are from simulations with increasing amounts of attenuation and all other material properties equal to those of isopropanol. In all cases, the value of the ratio $u_2/(xu_0^2)$ approaches the same limit as the propagation distance x goes to zero.

In the limit of the propagation distance going to zero, all of the attenuation terms become negligible and the utility of eqn 2 can be extended to cases involving attenuation loss,

$$\lim_{x \rightarrow 0} \frac{p_2(x)}{xp_0^2} = \frac{\beta\omega}{2\rho_0c_0^3} = \text{constant} \quad (4)$$

Solving eqn 4 for the nonlinearity parameter one obtains

$$\beta = \frac{2\rho_0c_0^3}{\omega} \left. \frac{p_2(x)}{xp_0^2} \right|_{x \rightarrow 0} \quad (5)$$

or in units of particle velocity,

$$\beta = \frac{2c_0^2}{\omega} \left. \frac{u_2(x)}{xu_0^2} \right|_{x \rightarrow 0} \quad (6)$$

These forms permit the determination of the nonlinearity parameter by extrapolating experimental data back to zero propagation distance, without a detailed knowledge of the attenuation properties of the host medium.

As implemented by Law *et al.* 1981, eqn 5 requires knowledge of the absolute levels of fundamental and second harmonic pressure amplitudes (p_0 and p_2). It is possible to obtain the absolute values of pressure by using a calibrated receiver, but this is often not feasible. An alternative approach is to perform a relative measurement by comparing the results obtained with the material under test to those obtained with a reference material whose nonlinearity parameter is known. By assuming a value for the nonlinearity parameter β in water, several researchers have successfully measured the value of β in a range of fluids (Adler and Hiedemann, 1962; Banchet *et al.*, 2000; Banchet and Cheeke, 2000; Dong *et al.*, 1999; Germain *et al.*, 1989; Gong *et al.*, 1984; Gong *et al.*, 1989; Law *et al.*, 1985, 1981; Saito *et al.*, 2005; Shklovskaya-Kordi, 1963), biological tissues (Gong *et al.*, 1984; Gong *et al.*, 1989; Law *et al.*, 1985, 1981), tissue mimicking phantoms (Dong *et al.*, 1999) and ultrasonic contrast agents (Wu and Tong, 1998).

The square of the signal from a transducer measuring the ultrasonic field, is proportional to the product of the pressure and particle velocity amplitudes,

$$\begin{aligned} |V_1|^2 &= \frac{T_1^I}{K_1} (p_1 \bullet u_1) \\ |V_2|^2 &= \frac{T_2^I}{K_2} (p_2 \bullet u_2) \end{aligned} \quad (7)$$

Here K_1 and K_2 are constants representing the electromechanical transfer function of the receiving transducer at the fundamental and second harmonic frequencies, respectively. T^I represents the frequency independent intensity transmission coefficient from the ultrasonic source into the fluid being measured,

$$T^I = \frac{4Z_1 Z_2}{(Z_1 + Z_2)^2} \quad (8)$$

In this case, the acoustic impedance Z_1 and Z_2 are the product of the mass density and the sound velocity for the steel delay line and the fluid under investigation, respectively. Multiplying eqn 5 and eqn 6, one obtains

$$\beta^2 = \frac{4\rho_0 c_0^5}{\omega^2} \left. \frac{p_2(x) u_2(x)}{x^2 p_0^2 u_0^2} \right|_{x \rightarrow 0} \quad (9)$$

Substituting the relationships for the measured quantities, as defined in eqn 7, and factoring out the intensity transmission coefficient term, we obtain

$$\beta^2 = \frac{4\rho_0 c_0^5}{\omega^2} T^I \left. \frac{K_{2f} |V_{2f}(x)|^2}{x^2 (K_{1f} |V_{1f}(0)|^2)^2} \right|_{x \rightarrow 0} \quad (10)$$

Equation 10 is valid for both the sample and the reference, so taking the ratio of β^2 for the sample to β^2 of the reference, canceling the electro-mechanical transfer function constants K_1 and K_2 , and introducing the notation Φ_{sample} and $\Phi_{\text{reference}}$ for the limit of the ratios of the measured quantities,

$$\Phi_{\text{sample}} \equiv \left. \frac{|V_{2f}^s(x)|^2}{x^2 (|V_{1f}^s(0)|^2)^2} \right|_{x \rightarrow 0}, \quad \Phi_{\text{reference}} \equiv \left. \frac{|V_{2f}^r(x)|^2}{x^2 (|V_{1f}^r(0)|^2)^2} \right|_{x \rightarrow 0} \quad \text{one obtains,} \quad (11)$$

$$\frac{\beta_{\text{sample}}^2}{\beta_{\text{reference}}^2} = \frac{\rho_s c_s^5}{\rho_r c_r^5} \frac{T_s^I}{T_r^I} \frac{\Phi_{\text{sample}}}{\Phi_{\text{reference}}} \quad (12)$$

This can be rewritten to solve for the unknown coefficient of nonlinearity,

$$\beta_{\text{sample}} = \beta_{\text{reference}} \sqrt{\frac{\rho_s c_s^5}{\rho_r c_r^5} \frac{T_s^I}{T_r^I} \frac{\Phi_{\text{sample}}}{\Phi_{\text{reference}}}} \quad (13)$$

The values of B/A are then calculated using the relationship $\beta = 1 + \frac{B}{2A}$

METHODS

Experimental Approach

The experimental approach developed and implemented in this work can be viewed as a hybrid approach combining aspects of the pullback method (Law *et al.*, 1985, 1981) and the substitution method (Dong *et al.*, 1999; Gong *et al.*, 1989; Saito *et al.*, 2005; Shklovskaya-Kordi, 1963). In this work, a stainless-steel delay line is used to position the focal zone associated with the fundamental frequency component in the liquid sample volume (Wallace *et al.*, 2004). The receiving transducer is immersed in the liquid sample, and the amplitude of the fundamental and second harmonic components are measured as a function of propagation distance. These data are reduced to determine the nonlinear parameter B/A , the small-signal speed of sound, and the attenuation coefficient.

A scaled diagram of the experimental apparatus is shown in Fig. 2. The ultrasonic source, a contact transducer (Panametrics V311 planar, 1.27 cm diameter, 10 MHz center frequency), is coupled to the bottom of a polished stainless-steel cylinder with a thin vacuum grease bond. A plastic (Delrin™) ring is attached to the top of the steel cylinder that compresses an o-ring and forms a sealed basin to hold the fluid sample under test. This assembly (contact transducer, steel cylinder, and plastic sample chamber) is positioned on top of a gimbaled plate, for leveling and alignment purposes. The receiving immersion transducer (Panametrics V316 planar, 3 mm diameter, 20 MHz center frequency) is attached to a search tube that is in turn connected to the X , Y , and Z -axes of a motion control system. The receiving transducer can be immersed into the fluid mixture with the distance between the steel-liquid interface and the face of the receiver controlled by the Z -axis of the motion control system, with a spatial resolution of twenty microns.

The steel cylinder delay line was cut from an 8.9 cm diameter extruded solid cylindrical stock of type 304 stainless-steel. The faces of the cylinder were machined flat and parallel, and polished smooth. In addition to serving as the bottom of the liquid sample chamber, the steel cylinder functions as an ultrasonic delay line. The experiment is designed to position at the steel-liquid interface the focal zone of the fundamental ($1f$) frequency component that is transmitted by the contact transducer. The distance to the natural focus, N , is given by,

$$N = \frac{D^2}{4\lambda} \left(1 - \left(\frac{\lambda}{D} \right)^2 \right) \approx \frac{D^2}{4\lambda} \quad (14)$$

Here, D is the diameter of the transducer and $\lambda = c_0 / f$ is the ultrasonic wavelength (Kinsler *et al.*, 2000). Prior to the assembly of the sample chamber, the thickness of the steel cylinder was measured with Vernier calipers to be 4.64 cm. The speed of sound in the stainless-steel was then determined to be 5730 m/s using the contact transducer in a pulse echo mode to measure the round-trip time of flight for an ultrasonic pulse inside the steel.

Use of a stainless-steel delay line in conjunction with the contact transducer offers two significant advantages over previously mentioned methods. First, because the speed of sound in steel is approximately four times faster than water, the diffraction pattern is effectively “compressed” so that the distance to focal zone in steel is approximately one quarter the corresponding distance in water. Second, the harmonic distortion of the finite amplitude wave is substantially reduced with the stainless-steel delay line as compared to that obtained with an equivalent length all-water path (Wallace *et al.*, 2004).

Sample preparation

In preparation for the ultrasonic investigation, eleven different concentrations of isopropyl alcohol and water were formulated to span the range from pure water to pure alcohol, as suggested by the work of Sehgal *et. al.* 1986 . Table 1 lists the volume percent and molar percent fractions in each sample. The solutions were prepared by volume in 400 cm³ quantities and stored in sealed Nalgene™ containers for subsequent use. The sample chamber defined by the steel cylinder and the plastic ring holds approximately 55 cm³ of liquid, thus permitting multiple chamber dosings from each 400 cm³ volume prepared. Production of relatively large total volumes improved the precision of the volume concentration preparations and facilitated reproducibility of the measurements. The fluid sample chamber was dosed using a clean 25 cm³ serological pipette. After the ultrasonic measurements, the same pipette was used to drain and discard the fluid sample.

The temperature in the liquid sample volume was monitored continuously throughout the experiment and a value was recorded with each radio-frequency waveform acquisition. A thermistor (Omega OL-710) was inserted through a port in the center of the chamber wall, and measurements were made with a thermistor thermometer (Omega 5831A). The thermistor thermometer has an analog voltage output that is linearly proportional to the temperature. This voltage was monitored by a digital multimeter (Hewlett-Packard HP 3478A) interfaced to the data acquisition computer (Apple G3/300). The temperature was maintained at 21°C ± 1°C during the experimental measurements.

Compensating for transmitted harmonics

Measurements of the nonlinearity parameter, B/A , for each of the isopropanol concentrations, require the determination of the intercept of the ratio of the measured second harmonic power squared to the fundamental power squared and distance squared in the limit of zero propagation distance, as expressed in eqn 11. Because of the effects of attenuation, one anticipates that a plot of the ratio of terms in eqn 11 as a function of propagation distance, x , will be a decaying exponential. If the plot has no offset in measured second harmonic values, then a plot of this ratio as a function of distance would be a straight line on a log-linear plot. If, however, there is a small initial second harmonic amplitude present (e.g., undesired harmonic signal transmitted by the source transducer, or generated in the stainless-steel delay line), then the plot of this ratio will not be a straight line. A computation package that uses the Burgers' equation enhanced angular spectrum approach was used to simulate this effect (Christopher and Parker, 1991; Vecchio and Lewin, 1994). This approach permits the modeling of both the propagation and the distortion of a diffracting ultrasonic signal. The results of a simulation are presented in Fig. 3, where the ideal case of propagation in water and isopropanol with no transmitted second harmonic is compared with a situation where there is a small (60 dB below the fundamental) initial contribution to the second harmonic power.

Fig. 3(a) shows the results of a simulation of the fundamental and second harmonic components propagating in either an isopropanol or a water medium, with and without the additional initial second harmonic contribution. The -60 dB initial second harmonic is observed to act as an additive value to the second harmonic curve, defining a lower limit. In Fig. 3(b) the impact of this initial second harmonic contribution on the ratio Φ is to "turn-up" the curve for small values of the propagation distance. At larger values of the propagation distance, the values of the ratio Φ for the curves, with and without the additional second harmonic, coincide. To avoid any such problems in curve fitting experimental data of this sort, the axial range of the curve fit was restricted to values between 1.0 and 2.1 cm for all concentrations.

Data acquisition

To measure the coefficient of nonlinearity for an isopropanol-water mixture, the amplitudes of the fundamental ($1f$) and second harmonic ($2f$) components of the transmitted ultrasound as a function of propagation distance need to be determined, in addition to the mass density and the speed of sound of the mixture. The mass density of pure water and pure isopropanol were taken to have the accepted values of 1.0 gm/cm^3 and 0.785 gm/cm^3 , respectively. The mass density of the mixtures were assumed to follow a simple law of mixtures,

$$\rho_{\text{mixture}} = \frac{(\rho_{\text{water}})(\text{Volume}_{\text{water}}) + (\rho_{\text{alcohol}})(\text{Volume}_{\text{isopropanol}})}{(\text{Volume}_{\text{total}})} \quad (15)$$

The speed of sound in the mixtures and the amplitude of the $1f$ and $2f$ components were determined from the same pullback measurement. In addition, the acoustic impedance was determined from $Z = \rho c$ for the steel delay line (45 MRayls) and for each sample (which ranged from 0.8 to 1.5 MRayls). The impedance of the receiving transducer was experimentally determined to be 5 MRayls.

The transmitted signals were generated by sending a $4.0 \mu\text{s}$ long tone burst, gated from a 7 MHz continuous wave tone generated by a signal generator (Hewlett-Packard HP 606B), to the transmitting transducer. The transmitted ultrasonic signal was measured with the receiving immersion transducer, whose output was fed directly into the 50Ω input of a digital oscilloscope (Tektronix 2440). To enhance the signal-to-noise ratio, 128 acquired 1024-point time domain waveforms were temporally averaged. The received signals were digitized at a 250 MS/s sampling rate, giving a total trace length of $4.096 \mu\text{s}$. In each record, there existed a baseline at the beginning to permit timing measurements as well as approximately 25 equivalent cycles of the 7 MHz tone burst in each digitized trace. Data were collected at a total of 69 axial positions, spaced 0.25 mm apart, from 4.0 to 21.0 mm as measured from the steel-liquid interface. Separations of less than 4.0 mm would not be valid due to reverberations between the receiver and the steel. All axial positions were obtained by moving the receiving transducer in only one direction to avoid errors associated with backlash. The entire experiment, with all eleven water-isopropanol concentrations, was repeated in three separate acquisitions. The received signal at each axial position demonstrated characteristics of weak nonlinearity and plane wave propagation that were verified experimentally and through simulation (Wallace *et al.*, 2004).

RESULTS

Velocity

Measurements of the velocity for each concentration of isopropanol and water were obtained by determining the time shifts associated with the maximum correlation of the time domain traces that correspond to precisely known differences in axial position. Fig. 4 illustrates the measured velocity values as a function of isopropanol and water concentrations. The closed circles represent the average measured values of the three separate experimental measurements. Values of the standard deviation for each concentration are plotted, but are smaller than the symbol diameter. The open circles represent published values of the velocity reported by Sehgal *et al.* 1986. Good agreement is found between our measured values and those previously published values, obtained with a thermodynamic method, at all concentrations of isopropanol and water.

Attenuation

Fitting a decaying exponential to the measured power in the fundamental frequency component of the transmitted signal as a function of propagation distance provided an estimate of the attenuation coefficient at the fundamental frequency. The loss of energy in the fundamental (1f, 7 MHz) component of the transmitted field due to generation of higher harmonic frequencies were neglected because of the nature of working in the weakly nonlinear regime. The results of these attenuation coefficient estimates for each concentration are plotted in Fig. 5. Upon examination, the maximum attenuation appears to occur at an approximately forty percent volume concentration of isopropanol in water. This result is consistent with the ultrasonic measurements of mixtures of alcohol and water reported by Burton (1948) and Storey (1952).

Nonlinear Parameter

Table 2 lists the average measured values for the nonlinear parameter B/A , as well as the speed of sound and the attenuation coefficient, as a function of volume concentration for mixtures of water and isopropanol. Estimates of the nonlinearity parameter β were determined for each of the concentrations using eqn 13. These reported values represent the average of the three independent data acquisition runs. The measured mean and standard deviation values of the nonlinear parameter B/A are plotted in Fig. 6 as a function of isopropanol-water concentration. Good agreement is observed between this investigation's measured values and the values reported by Sehgal *et al.* 1986 with a thermodynamic method. The error estimates range from less than 2% to 11%, with an average uncertainty in the measurement technique of 4.4%. It is interesting to note that the measurements with the largest uncertainties correspond to the sample mixtures with the highest values of attenuation (40% and 60% isopropanol).

The data sets of Fig. 6 are plotted against each other in Fig. 7(a), and the value of the square of the linear correlation constant, r , is determined. The indicated value of 0.99 indicates a strong correlation between the two sets of data. Fig. 7(b) shows a Bland-Altman analysis of the data (Bland and Altman, 1986). Again, good agreement is noted between the two sets of data.

DISCUSSION

An enhanced experimental approach, designed to measure the nonlinear parameter B/A , the small-signal speed of sound, and the attenuation coefficient, was presented. This finite amplitude technique was successfully employed to study the linear and nonlinear ultrasonic properties in eleven different mixtures of isopropyl alcohol (isopropanol) and water. Good agreement for all ultrasonic parameters was found among repeated independent measurements, as well as between our measurements and values reported in the literature (Sehgal *et al.*, 1986), which were acquired using a thermodynamic technique. An overall relative accuracy of ~ 5% in our measurements compares quite favorably with the range of measurement techniques reported in the literature (Beyer, 1998).

It is interesting to note that the results for the attenuation and velocity measurements suggest a Kramers-Krönig-like relationship exists between them, with the maximum rate of change in the attenuation coefficient corresponding to the maximum value of velocity (Waters *et al.*, 2005). Madigosky and Warfield (1987) observed that "the absorption maximum often occurs near the composition at which other properties such as viscosity, heat of mixing, partial molar volume, and freezing point also exhibit maxima or minima." Molecular relaxation processes associated with these binary mixtures are discussed by Bhatia (1985).

These results suggest that the experimental technique described here can be applied to characterize the intrinsic nonlinear and linear properties of a wide range of fluids and fluid-

mixtures. With modest modification, similar methods can be adapted to investigate the properties of intact biological tissues *in vitro*. In this case, where the tissue specimen of interest is not amenable to the pullback method utilized for the liquid, then (provided the attenuation and velocity are known independently) a calibrated receiver can be used to estimate the nonlinear parameter with a measurement at a single through-transmission location. The physics describing the propagation of a finite amplitude ultrasonic wave also underpins the improvements in image quality associated with the development of harmonic imaging in clinical echocardiography. Therefore, this work contributes to developments that, in the long term, may contribute to future improvements in diagnostic ultrasound, including potential determination of the nonlinear properties of tissue *in vivo* (Fujii *et al.*, 2004).

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References

- Adler L, Hiedemann EA. Determination of the nonlinearity parameter B/A for water and m-xylene. *J Acoust Soc Am* 1962;34:410–412.
- Banchet J, Cancian J, Cheeke JDN. Measurement of the acoustic nonlinearity parameter in 1-alkanols. *Ultrasonics* 2000;38:301–304. [PubMed: 10829678]
- Banchet J, Cheeke JDN. Measurement of the acoustic nonlinearity parameter B/A in solvents: Dependence on chain length and sound velocity. *J Acoust Soc Am* 2000;108:2754–2758.
- Beyer, RT. The parameter B/A. In: Hamilton, MF.; Blackstock, DT., editors. *Nonlinear Acoustics*. San Diego, CA: Academic Press; 1998. p. 25–40.
- Bhatia, AB. New York: Dover Publications, Inc; 1985. *Ultrasonic Absorption: An introduction to the theory of sound absorption and dispersion in gases, liquids, and solids*.
- Bjorno L. Characterization of biological media by means of their non-linearity. *Ultrasonics* 1986;24:254–259. [PubMed: 3750552]
- Blackstock, DT.; Hamilton, MF.; Pierce, AD. Progressive Waves in Lossless and Lossy Fluids. In: Hamilton, MF.; Blackstock, DT., editors. *Nonlinear Acoustics*. Vol. 1998. San Diego, CA: Academic Press; p. 65–150.
- Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307–310. [PubMed: 2868172]
- Burton CJ. A study of ultrasonic velocity and absorption in liquid mixtures. *J Acoust Soc Am* 1948;20:186–199.
- Christopher PT, Parker KJ. New approaches to nonlinear diffractive field propagation. *J Acoust Soc Am* 1991;90:488–499. [PubMed: 1880298]
- Dong F, Madsen E, MacDonald M, Zagzebski J. Nonlinearity parameter for tissue-mimicking materials. *Ultrasound Med Biol* 1999;25:831–838. [PubMed: 10414900]
- Fujii Y, Taniguchi N, Akiyama I, Tsao J-W, Itoh K. A new system for in vivo assessment of the degree of nonlinear generation using the second harmonic component in echo signals. *Ultrasound Med Biol* 2004;30:1511–1516. [PubMed: 15588961]
- Germain L, Jacques R, Cheeke JD. Acoustic microscopy applied to nonlinear characterization of biological media. *J Acoust Soc Am* 1989;86:1560–1565. [PubMed: 2808915]
- Gong X-F, Ruo F, Cheng-ya Z, Tao S. Ultrasonic investigation of the nonlinearity parameter B/A in biological media. *J Acoust Soc Am* 1984;76:949–950.
- Gong X-F, Zhu Z-M, Shi T, Huang J-H. Determination of the acoustic nonlinearity parameter in biological media using FAIS and ITD methods. *J Acoust Soc Am* 1989;86:1–5. [PubMed: 2754102]
- Kinsler, LE.; Frey, AR.; Coppens, AB.; Sanders, JV. *Fundamentals of Acoustics*. 4. New York: John Wiley and Sons, Inc; 2000.
- Law WK, Frizzell LA, Dunn F. Ultrasonic determination of the nonlinearity parameter B/A for biological media. *J Acoust Soc Am* 1981;69:1210–1212.

- Law WK, Frizzell LA, Dunn F. Determination of the nonlinearity parameter B/A of biological media. *Ultrasound Med Biol* 1985;11:307–318. [PubMed: 4035807]
- Madigosky WM, Warfield RW. Sound absorption and concentration fluctuations in water-propanol mixtures. *J Chem Phys* 1987;86:1491–1496.
- Saito S. Measurement of the acoustic nonlinearity parameter in liquid media using focused ultrasound. *J Acoust Soc Am* 1993;93:162–172.
- Saito S. Property of the nonlinearly generated second-harmonic component of focused ultrasound detected by a concave receiver. *Ultrasonics* 1996;34:537–541.
- Saito S, Yamamoto A, Nakamura K. B/A Measurement for Liquid Media Using an LN Transducer with Inverted-Domain Layer. *Jpn J Appl Phys* 2005;44:4431–4435.
- Sehgal CM, Porter BR, Greenleaf JF. Ultrasonic nonlinear parameters and sound speed of alcohol-water mixtures. *J Acoust Soc Am* 1986;79:566–570. [PubMed: 3950207]
- Shklovskaya-Kordi VV. An acoustic method of determining the internal pressure in a liquid. *Sov Phys Acoust* 1963;9:82–85.
- Storey LRO. Ultrasonic absorption in mixtures of ethyl alcohol and water. *Proc Phys Soc London, Sect B* 1952;65:943–950.
- Vecchio CJ, Lewin PA. Finite Amplitude Acoustic Propagation Modeling Using the Extended Angular Spectrum Method. *J Acoust Soc Am* 1994;95:2399–2408.
- Wallace KD, Holland MR, Miller JG. Novel approach for overcoming effects of diffraction in measurements of the nonlinear B/A parameter in liquidlike media. *J Acoust Soc Am* 2004;116:2566.
- Waters KR, Mobley J, Miller JG. Causality-imposed (Kramers-Kronig) relationships between attenuation and dispersion. *IEEE Trans Ultrason Ferroelectr Freq Control* 2005;52:822–823. [PubMed: 16048183]
- Wu J, Tong J. Measurements of the nonlinearity parameter B/A of contrast agents. *Ultrasound Med Biol* 1998;24:153–159. [PubMed: 9483783]

Figure 1.

Results of simulations showing the values for the left side of eqn 3, for isopropanol (0.804 gm/cm³ mass density, 1220 m/s speed of sound, 11.8 nonlinear B/A parameter, and frequency dependence of attenuation proportional to square of the frequency), with the specified values of attenuation at a fundamental frequency of 7.0 MHz. In the limit of no axial propagation, the ratio is fixed.

Figure 2.

Diagram of the axial pullback measurement apparatus. The transmitter is a 1.27 cm contact transducer, while the receiver is a 0.3 cm immersion transducer that is translated 1.7 cm through the sample. A thermistor is attached through a port on the side of the chamber wall. Simulation of the 7 MHz fundamental ($1f$) field component is shown inside the delay line.

Figure 3.

Results of simulations illustrating the impact of having an initial (nonzero) second harmonic component (14 MHz), for both water (1.00 gm/cm³ mass density, 1480 m/s speed of sound, 5.0 nonlinear B/A parameter, and frequency dependence of attenuation proportional to square of the frequency) and isopropanol (see Fig 1 caption for assumed material parameters). (a) Results from the simulation showing the power in the fundamental and second harmonic as a function of axial distance. The case of no initial second harmonic is compared with the case where a small (-60 dB re:1f) initial second harmonic component is present. (b) The ratio Φ , when a small initial second harmonic component is present illustrating extrapolation errors in the regime of small axial distance.

Figure 4.

Plot of the measured velocity for eleven different concentrations of isopropanol and water. Standard deviation error bars are shown, but are smaller than the symbol size. Open symbols correspond to the values published by Sehgal *et al.* 1986 .

Figure 5. Measured values (mean $\pm$ standard deviation) of the attenuation coefficient and speed of sound at the 7 MHz fundamental frequency.

Figure 6.

Measured values (mean $\pm$ standard deviation) of the nonlinear parameter B/A for eleven different concentrations of isopropanol and water. The open squares are from measurements reported by Sehgal *et al.* 1986.

Figure 7.

(a) Measured values of the nonlinear parameter B/A versus those of Seghal *et. al.* 1986 . The square of the linear correlation coefficient is also given. (b) The difference in B/A as determined by the two methods compared to their mean. The average value of the difference, as well as two times the standard deviation of the difference, is also illustrated.

TABLE 1

Concentrations of isopropyl alcohol and water solutions investigated. The molecular weights of water (H₂O) and isopropanol (C₃H₈O₂) are 18.01 and 60.10 Da, respectively.

Concentration Number	Volume Percent Water	Volume Percent Isopropanol	Mole Percent Water	Mole Percent Isopropanol
1	100 %	0 %	100 %	0 %
2	95 %	5 %	98.8 %	1.2 %
3	90 %	10 %	97.4 %	2.6 %
4	85 %	15 %	96.0 %	4.0 %
5	80 %	20 %	94.4 %	5.6 %
6	75 %	25 %	92.7 %	7.3 %
7	70 %	30 %	90.8 %	9.2 %
8	60 %	40 %	86.4 %	13.6 %
9	40 %	60 %	73.8 %	26.2 %
10	20 %	80 %	51.4 %	48.6 %
11	0 %	100 %	0 %	100 %

TABLE 2

Tabulation of the experimentally determined values of the speed of sound, the attenuation, and the nonlinear parameter B/A for all isopropanol concentrations. Also shown is the standard deviation associated with B/A as well as the percent error of B/A . The average uncertainty associated with measuring B/A was found to be 4.4%.

Isopropanol Concentration	Speed of Sound (m/s)	Attenuation (cm^{-1})	Nonlinear Parameter B/A	Standard Deviation of B/A	Percent Error (S.D. / Mean) * 100%
0%	1490.40	$4.04 * 10^{-3}$	5.00	-	-
5%	1527.60	$5.26 * 10^{-3}$	4.80	0.09	1.8%
10%	1562.70	$1.31 * 10^{-2}$	4.64	0.13	2.8%
15%	1597.40	$1.58 * 10^{-2}$	4.85	0.26	5.3%
20%	1622.00	$2.27 * 10^{-2}$	5.24	0.23	4.4%
25%	1630.30	$6.72 * 10^{-2}$	6.12	0.11	1.8%
30%	1610.50	0.183	7.04	0.26	3.7%
40%	1549.50	0.351	9.71	1.08	11%
60%	1415.80	0.240	11.4	0.84	7.4%
80%	1295.20	$9.75 * 10^{-2}$	11.9	0.23	1.9%
100%	1162.40	$4.22 * 10^{-2}$	11.8	0.38	3.3%
Average percent error for all of the measurements of the nonlinear parameter B/A :					4.4%