DETERMINATION OF THE *B/A* OF BIOLOGICAL MEDIA BY MEASURING AND MODELING NONLINEAR DISTORTION OF PULSED ACOUSTIC WAVE IN TWO-LAYER MEDIA

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The acoustic nonlinearity parameter, B/A, is a fundamental material constant characterizing nonlinear properties of biological media. Knowledge of the B/A of biological fluids or soft tissues through which pulsed acoustic waves generated from clinically relevant probes are propagating is necessary whenever high intensity pressure fields are produced. The numerical model recently developed in our lab, capable of predicting the pulsed sound fields generated from axisymmetric sources in nonlinear attenuating media, was a powerful instrument for investigating nonlinear acoustic fields produced from circular plane or focused sources in attenuating media in dependence on boundary condition parameters. Quantitative analysis of the obtained results enabled developing the alternative method for determination of the B/A parameter of biological media. First, the method involves measuring in the near field of a piezoelectric transducer the nonlinear waveform distortion of the pulsed acoustic wave propagating through the two-layer system of media: water-tested material. Then, the method involves numerical modeling, in frequency domain and under experimental boundary conditions, the nonlinear waveform distortion of the propagating wave by using the Time-Averaged Wave Envelope (TAWE) approach [1]. The obtained numerical simulation results were fitted to the experimental data by adjusting the B/A parameter of the tested material. The determined values of the B/A for standard media considered (corn oil, glycerol, pig blood, homogenized pig liver), whose density, sound velocity and attenuation law have been preliminary determined experimentally, are in a good agreement with those published. The proposed method ensure the decimal degree of accuracy, is relatively simple to use and requires small volume of tested materials that is important because of difficulty of their availability.

INTRODUCTION

Nonlinear effects incidental to a finite-amplitude acoustic wave propagation in thermoviscous fluids are systematically studied theoretically and experimentally in many laboratories around the world because of extensive possibilities of their practical applications, especially for medical purposes [2, 8-10]. Propagation of high intensity ultrasound waves in biological media is a nonlinear phenomenon. Nonlinearity of media is characterized by their material constant, the second order acoustic nonlinearity parameter, *B/A*. Value of the *B/A* determines waveform distortion level of the sound wave propagating through the nonlinear attenuating medium due to native generation of harmonic frequencies. Knowledge of the *B/A* parameter of media through which the wave propagates is necessary for predicting nonlinear pressure fields in soft tissues in order to assess safety of modern US medical equipment or to improve image quality using the Tissue Harmonic Imaging (THI) technique. For example, recently Verma *et al.* [3] showed that applying 3D THI technique in obstetrics high level of nonlinear waveform distortion may occur. Then harmonic frequencies are generated in the nonlinear acoustic beam penetrating highly attenuating soft tissues whose attenuation increases with the frequency and can lead to significant temperature rises [4]. Also therapeutic ultrasound techniques, such as the High Intensity Focused Ultrasound (HIFU) or lithotripsy produce the nonlinear waveform distortion leading to enhanced local heating and thermal ablation of tissues at the focal region [5, 6].

Among hitherto existing methods for determination of the *B/A* of pure liquids, two methods in particular, have found application for biological media: thermodynamic and finite-amplitude methods [7]. In the thermodynamic method the parameter *B/A* is determined by measuring changes in the sound velocity resulting in changes of the pressure and temperature for the constant temperature and pressure, respectively. Experimental determination of the parameter *B/A* of media using a finite-amplitude method involves measuring the second harmonic amplitude of an acoustic wave distorted during propagation through the tested medium. Both methods are based on simplified mathematical models assuming propagation of the plane continuous acoustic wave in a lossless fluid as well as on the discrete measuring that utilize the fixed path-length technique. All methods mentioned have limitations and ensure for accuracy rarely better than ± 5% for liquids and ± 10 % for soft tissues.

The purpose of this work was to develop a relatively simple method for determining with a decimal accuracy the nonlinearity parameter, *B/A*, of biological liquids or soft tissues. The proposed method is based on the comparison of the nonlinear waveform distortion of the pulsed acoustic wave, propagating through the two-layer system of parallel media: water – tested material, numerically modeled in frequency domain and under experimental boundary conditions, with the experimental data. Water is used as the reference medium with known nonlinear properties in order to calibrate the experimental setup. The numerical model used accounts for the effects of absorption, diffraction, nonlinear interaction of harmonics as well as for the reflection and transmission at the media interfaces. The boundary condition parameters, namely the source pressure amplitude, initial acoustic pulse waveform, radiating aperture apodisation function as well as the tested material density, sound velocity, frequency-dependent attenuation law are determined by preliminary measuring. The measured boundary condition parameters are the input data to the numerical model.

First, the method involves measuring the linear propagation of the pulsed tone burst in water and fitting the theoretical results obtained by means of linear theory to the experimental data by adjusting the source parameters: pressure amplitude at the surface, effective radius and radiating aperture apodisation function. Then, the method involves measuring the nonlinear waveform distortion of the acoustic pulsed wave propagating through water and fitting the numerically simulated results to the experimental data by matching the source boundary condition parameters. These preliminary measurements are required to calibrate the experimental setup. Next, the method involves measuring the nonlinear waveform distortion of the same tone burst propagating through the two-layer system of parallel media: water-tested material with the same path-length as in water. Finally, the method involves numerical modeling the nonlinear waveform distortion of the tone burst propagating through the two-layer system of media: water-tested material and fitting the theoretical results to the experimental data by adjusting the *B/A* value of the tested material.

1. NUMERICAL MODEL

The numerical model used for describing the nonlinear waveform distortion of the pulsed finite-amplitude sound pressure wave propagating in a thermoviscous medium accounts for the effects of diffraction, absorption and nonlinear interactions of harmonics and was comprehensively described in [1]. The model was made computationally efficient by replacing the conventional Fourier–series solution approach by the Time-Averaged Wave Envelope (TAWE) algorithm. The TAWE approach is based on decomposition of the propagating, nonlinearly distorted acoustic pulse or tone burst into a series of sinusoidal pulses with carrier frequencies being the harmonics of the initial (undistorted) acoustic pulse and with envelopes being the product of two specific functions. The first function represents the solution to the nonlinear wave equation under linear propagation conditions whereas the second function accounts for nonlinear interactions of harmonic components under given boundary conditions. Moreover the model accounts for the effect of reflections at the interfaces of multilayer system of media.

The computer implementation of the numerical model for axisymmetric cases in a form of the 3D (2D space + time) solver capable of predicting pulsed nonlinear acoustic fields from plane or focused circular acoustic sources in multilayer systems of parallel media with arbitrary attenuation law was a powerful research instrument for studying the properties of nonlinear acoustic fields produced in biological media for various boundary conditions. The boundary condition parameters were determined by the source shape, dimensions, operating conditions as well as by the linear and nonlinear parameters of media through which the finite-amplitude sound wave propagates. These parameters were introduced into the 3D solver as input data.

2. METHODS AND MATERIALS

The nonlinear waveform distortion of the pulsed finite-amplitude acoustic wave propagating through the attenuating medium is determined by properties of the acoustic field generated from the transducer as well as by linear and nonlinear qualities of the medium.

Thus, the transducer parameters required for the numerical model include the source pressure, effective radius, focal length, pressure waveform of the initial pulse, apodisation function, and pulse repetition period. The tested medium parameters required for the model are: density, sound velocity, small-signal attenuation coefficient at 1 MHz, attenuation frequency-dependence law and nonlinearity parameter, *B/A*. If boundary condition parameters of the transducer and linear parameters of the medium are determined experimentally then the *B/A* value of the medium can be determined by fitting the nonlinear waveform distortion of the wave propagating along the beam axis (simulated numerically in frequency domain) to the experimental data.

The principle of measuring the nonlinearity parameter *B/A* of the medium being examined involves:

1. determining the boundary condition parameters at the experiment temperature T for the medium being examined by measuring the density, ρ, sound velocity, c, small-signal attenuation coefficient, α, attenuation frequency-dependence law $\alpha(f)$;
2. determining the transducer parameters: effective radius a, pressure amplitude P_0 at the surface, initial acoustic pulse waveform and radiating aperture apodisation function by measuring the linear and nonlinear propagation of the tone burst in water and fitting the obtained experimental data to the numerically simulated results by adjusting the source boundary condition parameters. This preliminary measurements calibrate the experimental setup and ensure better accuracy of the proposed method;
3. measuring the nonlinear waveform distortion of the tone burst propagating through a two-layer media: water - tested material by using the method of the fixed path-length through the water layer and the variable path-length through the layer of the tested material;
4. introducing the input parameters into the numerical model and fitting the theoretical results obtained for two-layer system of media to the experimental data by adjusting the *B/A* value of the tested material.

A. Experimental setup

The experimental set-up used for the measurements is shown in Fig. 1.

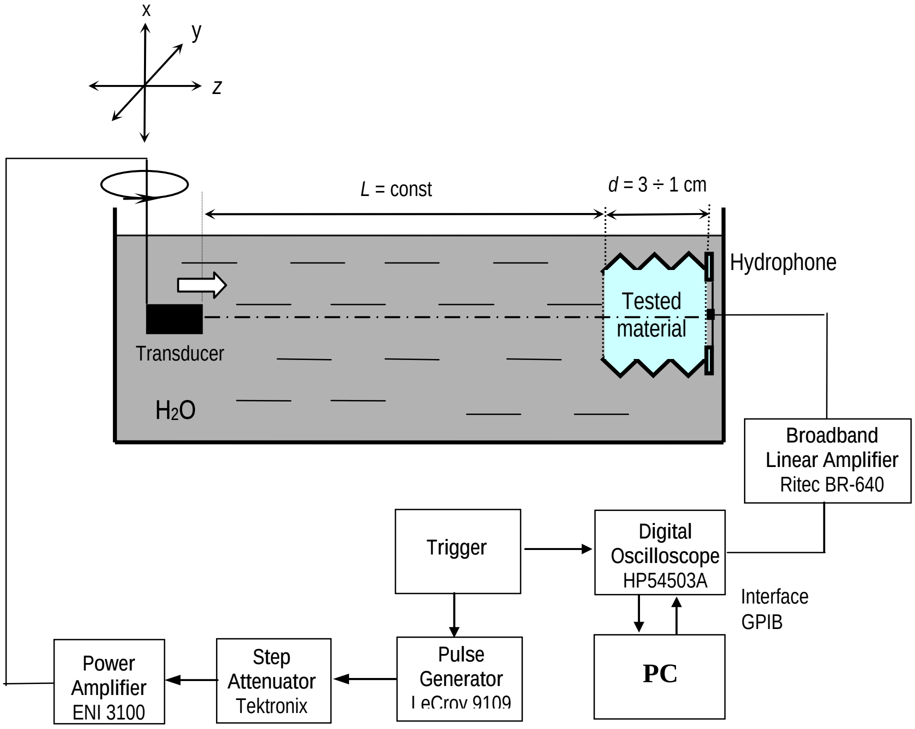

Fig.1 Schematic diagram of the experimental setup

The measurements were carried out at 25$^{\mathrm{o}}$ C temperature with a 20 mm diameter, 2 MHz central frequency, focused (focal length F = 80 mm) piezoceramic (Pz27 Ferroperm, Norway) transmitting transducer immersed in a temperature-controlled water. The transducer had a quarter-wavelength matching layer, was back-loaded and positioned on the translation stage driven by computer-controlled stepper motors allowing its motion in horizontal and vertical planes with varied steps (from 0.1 to 5 mm). The pressure pulse waveforms were measured by the broadband (calibrated up to 40 MHz) bilaminar polyvinylidene difluoride (PVDF) membrane hydrophone (Sonora Medical Inc. S/N S5-153, preamplifier P-159) with a 0.414 mm effective diameter of the active sensor element. The hydrophone was immersed in water and fixed on the acoustic axis. To maximise the signal to noise ratio at the measurement of the 20th harmonic the transducer were driven by 8-cycle tone bursts via RF Power Amplifier (ENI 3100LA, Rochester, NY, USA). The amplitude of the tone burst excitation voltage was controlled by the Step Attenuator (Tektronix 2701, Beaverton, OR, USA) to enable linear or nonlinear propagation. The frequency and duration of the tone bursts were adjustable using Arbitrary Function Generator (LeCroy 9109, Chestnut Ridge, NY, USA). At the low excitation level the transducer produced source pressure of 0.041 MPa. Nonlinear fields were produced by enhancing voltage at the output of the RF amplifier by a factor of 10 (producing source pressure of 0.41 MPa). The hydrophone output was additionally amplified by 20 dB using the linear broadband amplifier (Ritec BR-640, Warwick, RI, USA) and then fed to the input of an 8-bit digital oscilloscope (HP54503A, Hewlett Packard, Colorado Springs, CO, USA) with a 200 MHz sampling frequency. The received signals were digitised and averaged over 16 consecutive waveforms in the oscilloscope memory and then transferred for spectral analysis to 1.5 GHz clock frequency, 32-bit processor PC with 2 GB RAM. The amplitude of the measured harmonic components was corrected for the hydrophone sensitivity dependence on frequency.

B. Methodology of measurements

As noted above two excitation levels were used during measurements in water. Initially, the measurements were carried out at low excitation level (linear propagation mode). This was done in order to determine the acoustic axis as well as the input data to the numerical model.

The acoustic axis was accurately determined from symmetry of the acoustic beam patterns that were visualized as isobar contour lines. The input data included the acoustic parameters of water: density, ρ, sound velocity, c, small-signal attenuation coefficient, α_1, frequency-dependent attenuation law, $\alpha(f) = \alpha_1 \cdot f^2$, nonlinearity parameter, $B/A = 5.3$, as well as the transducer boundary condition parameters: effective radius, a, focal length, F, pressure amplitude P_0 at the surface (source pressure), pressure-time waveform, $P(t)$, of the initial tone burst that best reproduced the tone burst measured on the axis close to the transducer surface, radiating aperture apodisation function, $g(r)$, which produced the radial pressure distribution close to the transducer that best reproduced this measured.

The apodisation function $g(r)$, source pressure P_0 and pressure-time waveform $P(t)$ of the initial tone burst were determined at low excitation level by measuring the radial pressure distribution, its maximum and pressure-time waveform of the tone burst close to the radiating surface (5÷15 mm axial distance). Then the measured axial and lateral pressure distributions were compared with those theoretically predicted by the linear propagation theory accounting for the effect of attenuation while keeping the source pressure P_0 constant and varying the radiating aperture radius a and exponent m in the apodisation function $g(r)$.

The apodisation function was introduced into the model in analytical form:

$$g(r) = P_0 \left|1 - (r/a)^m\right|, \tag{1}$$

where, m denotes positive number that is determined by iteration process.

The pressure-time waveform of the initial tone burst was introduced to the numerical model in form of a polynomial function:

$$P(t) = (1 - |(t - t_c)/(t_s - t_f)|^n)\cdot\sin[\omega(t - t_c)] \qquad \text{for } t_s \le t \le t_f, \tag{2}$$

$$P(t) = 0 \qquad \text{for } t \not\subset (t_s, t_f).$$

(here, t_c, t_s, t_f is dimensionless time determining centre, start and finish points of the initial tone burst, n designates a positive number that is determined by iteration process.

In order to measure the nonlinear waveform distortion in water (nonlinear propagation mode) the excitation level of the transmitting transducer was increased 10 times (20dB). The value of P_0 in the numerical model was scaled up directly proportional to the applied excitation voltage and was equal to 0.41 MPa. At this level of excitation measuring the nonlinear waveform distortion in water were carried out on the acoustic axis. The measurement results were very repeatable. The measured axial pressure variations of the fundamental, 1st and 2nd harmonics were compared with those simulated numerically. Fig. 2 illustrates very good agreement between the calculated results and experimental data in water. The level of agreement determined by the pressure amplitude ratio of the fundamental to the 2nd harmonics as a function of the axial distance from the transducer face was equal to 0.96 ± 0.034 for all points measured. These results validated correctness and accuracy of the numerical model proposed and calibrated the experimental setup.

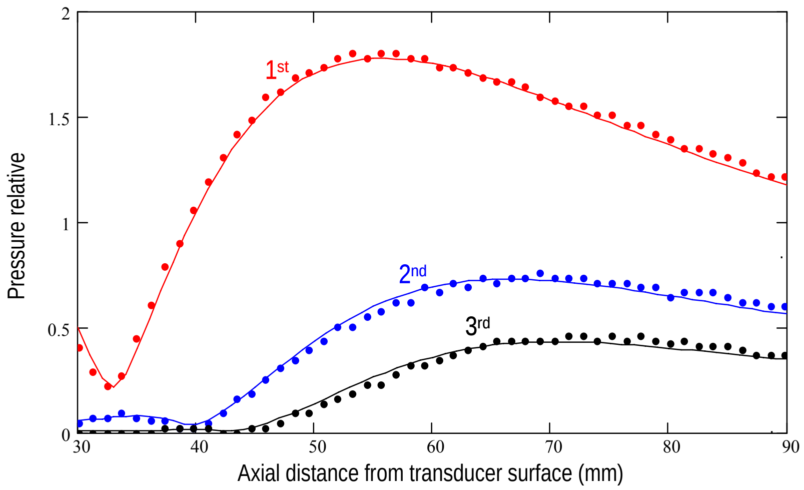

Fig.2 Axial variation of the fundamental (1st), 2nd and 3rd harmonics for the focused field in water. Fundamental frequency 2 MHz, source pressure 0.4 MPa. Experiment (points), theory (solid lines)

To measure nonlinear waveform distortion of the tone burst propagating through the two-layer system of parallel media: water – tested material the method of fixed path-length in water and variable path-length in tested material was used.

In previous publications [11, 12] the specific feature of pulsed nonlinear fields in water, generated from circular sources of the chosen dimensions and central frequency, was proved. Namely, the distance from the source at which the rapid building up of the second harmonics amplitude takes place is specific for this source, constant and does not dependent on the source pressure amplitude. This characteristic property of the nonlinear fields produced in water was used to develop an alternative method for determination of the parameter *B/A* of biological media.

The main principle of the proposed method is based on the numerical predicting the nonlinear waveform distortion of the tone burst propagating through the two-layer system of parallel media: water - tested material (in frequency domain and under experimental boundary conditions) and fitting the obtained numerical simulation results to the experimental data by adjusting the *B/A* parameter of the tested material.

For each source with chosen dimensions and frequency the thickness of the water layer in the two-layer system of media is specific for this source and equal to the axial distance from it at which rapid building up of the 2nd harmonics begins and the 3rd harmonics arises in water. For the transducer considered here this distance was found to be 45 mm (see Fig. 2). The thickness of the tested material layer may be chosen arbitrary, however soft tissues are highly attenuating media therefore their thickness was chosen no more than 5 centimetres.

To implement the experimental determining of nonlinear waveform distortion of the tone burst propagating through the two-layer system of parallel media: water- tested material the method of passing of the fixed path-length through the water and of the various path-length through the tested material was used. In order to realise the variable path-length of the tone burst through the tested material 5 cylindrical sample-holders filled up with this material were designed. Degassing of the tested material followed filling up the sample-holders. The sample-holders had the inside diameter of 7 cm and the variable height from 1 to 3 cm with 0.5 cm step. The input and output windows of the sample-holders were made of 20 μm thick, sound-permeable polyethylene foil stretched over each their end. The sample-holders were immersed in water between the transducer and hydrophone and located very close to the hydrophone at the fixed, 1 mm, axial distance from it by means of the specially designed holder enabling also the input and output windows to be parallel to the hydrophone plane. The 5 distorted electric signal waveforms were recorded by hydrophone, sampled and treated with the FFT. The amplitudes of obtained harmonics were corrected accordingly to the hydrophone frequency-dependent sensitivity characteristic (V/μPa) and fitted to those numerically predicted by adjusting the *B/A* value of the tested material. The numerical simulation results best fitted to the measured data determined the nonlinearity parameter of the medium under examination.

3. RESULTS

The standard liquids (corn oil, glycerol) and homogenised tissues (pig blood, pig liver) were considered as the tested materials. The linear and nonlinear acoustic parameters of these media are presented in Table 1.

Tab.1 Acoustic properties of the tested materials at temperature 25°C

Material	Density (kg/m^3)	Sound velocity (m/s)	Attenuation coefficient (Np/m · Hz^b)	*B*/*A* (literature)	Power-law *b*
Distilled degassed water	997	1497	$2.8 \cdot 10^{-14}$	5.3	2
Corn oil	920	1470	$70 \cdot 10^{-14}$	10.5	2
Glycerol	1260	1890	$570 \cdot 10^{-14}$	9.4	2
Pig blood	1080	1600	$16 \cdot 10^{-7}$	6.2	1.1
Homogenised pig liver	1060	1550	$78 \cdot 10^{-7}$	6.6	1

Numerical simulations were made when value of the *B/A* parameter for each tested material was varied around the nominal value known from literature between (B/A+1) and (B/A–1) with the increment $\Delta B/A = 0.5$

The numerically simulated axial pressure variation of the fundamental (1st), 2nd and 3rd harmonics of the 8-cycle tone burst generated from the source considered and propagating through the two-layer system of media including 40 mm of water and 50 mm of corn oil at the axial range from 45 to 75 mm is presented in Fig.3. For this case both the measured and simulated ratio of the 1st/2nd and 1st/3rd harmonics versus the axial range corresponding to the corn oil layer are shown in Fig. 4. The best correlation coefficient (0.986) between measured and calculated results was obtained when value of the parameter *B/A* for corn oil was equal to10. Similarly, the *B/A* value for glycerol was found to be 9, for homogenised pig liver 6.9, for pig blood 6.5.

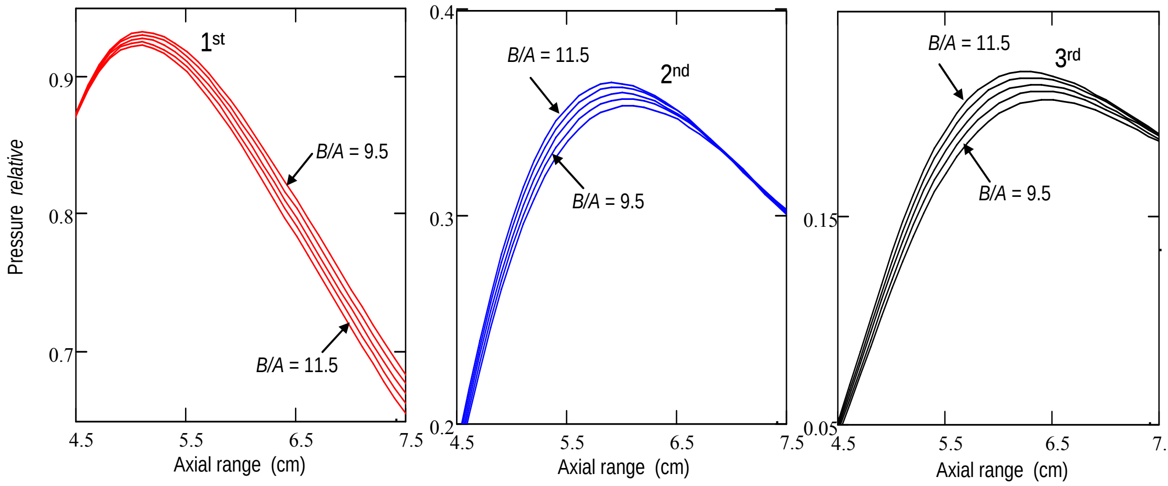

Fig.3 Simulated axial variation of the fundamental (1st), second (2nd) and third (3rd) harmonics of the 8-cycle tone burst with the initial pressure of 0.4 MPa generated from the circular focused source considered and propagating through the two-layer system of media: 4 cm water + 5 cm corn oil when the value of *B/A* for corn oil is adjusting from 9.5 to 11.5 with an increment of 0.5

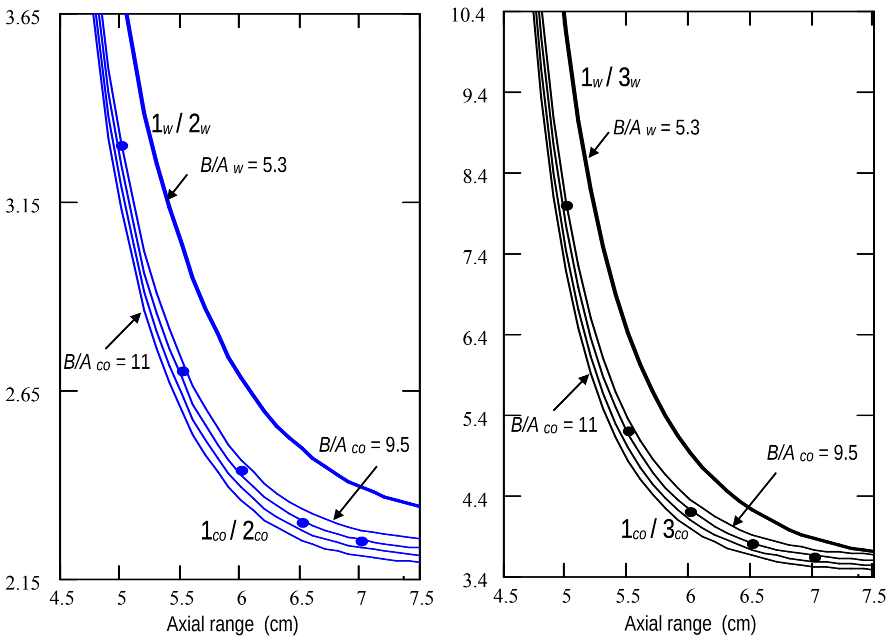

Fig.4 Axial variation of ratio of the 1st to 2nd and 1st to 3rd harmonics for the 8-cycle tone burst propagating through both the water, $(B/A)_w = 5.3$, or two-layer system of media: 4 cm water + 5 cm corn oil when the *B/A* of corn oil is adjusting from 9.5 to 11. Experiment (point), theory (solid lines)

4. DISCUSSION

The average values of the nonlinearity parameter measured for the standard materials considered are different from the values given in literature to within 4 %. The comparison of the experimental data and numerical simulation results has shown that our numerical model, based on the TAWE approach, is well suited to predict both the spatial-temporal and spatial-spectral pressure variations in the pulsed nonlinear beams produced from axisymmetric acoustic sources in multilayer biological media.

The accuracy of the proposed method depends on several factors. First, it depends on the accuracy of measurements of the boundary condition parameters being the input data to the numerical model, especially of the source pressure amplitude, apodisation function and attenuation frequency-dependence law of the tested medium. The variation of 1% in the source pressure leads to a variation of 3 % in determining the *B/A* value. Uncertainty in estimation of these parameters is the main reason of discrepancy between measured and predicted harmonics amplitudes. Therefore the proposed method involves the preliminary measurements of the nonlinear waveform distortion in water as the reference medium. These measurements enable to calibrate the experimental setup. Next, the accuracy of the proposed method depends on the accuracy of calibration of the hydrophone. The hydrophone used for measurements was calibrated in the limited range of frequencies (from 1 to 40 MHz). Thus, to maximise the number of experimentally generated harmonics (to within 20) that could be quantified using this hydrophone the transducer was chosen with the low, 2MHz central frequency. The following boundary condition parameters have the largest influence on the sensitivity of the method developed: source dimensions, pressure amplitude at the surface, central frequency. In order to increase the method sensitivity the source size and pressure at the surface should be increased, the central frequency should be decreased and the length of the sample with the tested material should be as long as possible. The determination of the *B/A* value of biological media with decimal accuracy requires maximising the transducer size and pressure amplitude at the surface as well as minimising the central frequency.

In conclusion, the proposed method is relatively simple and does not require large volume of the tested material. It is particularly important because of difficult availability of fresh biological tissues. The degree of accuracy of the method developed depends most of all on the accuracy of measurement of the source pressure, apodisation function and attenuation frequency-dependence law of the tested medium. Additionally, in order to increase accuracy of the proposed method the cylindrical sample-chamber of smoothly variable length should be used instead of 5 sample-holders of different length.

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