A review on B/A measurement methods with a clinical perspective

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A review on B/A measurement methods with a clinical perspective
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ABSTRACT:
The nonlinear parameter of ultrasound $B/A$ has shown to be a useful diagnostic parameter, reflecting medium content, structure, and temperature. Despite its recognized values, $B/A$ is not yet used as a diagnostic tool in the clinic due to the limitations of current measurement and imaging techniques. This review presents an extensive and comprehensive overview of the techniques developed for $B/A$ measurement of liquid and liquid-like media (e.g., tissue), identifying the methods that are most promising from a clinical perspective. This work summarizes the progress made in the field and the typical challenges on the way to $B/A$ estimation. Limitations and problems with the current techniques are identified, suggesting directions that may lead to further improvement. Since the basic theory of the physics behind the measurement strategies is presented, it is also suited for a reader who is new to nonlinear ultrasound. © 2021 Acoustical Society of America. https://doi.org/10.1121/10.0003627

I. INTRODUCTION

In the last several decades, ultrasound propagation has been treated as a nonlinear phenomenon (Duck, 2002). The importance of nonlinear propagation effects has been recognized in medical ultrasound for predicting/modelling heat deposition in tissue, relevant for safety regulations, as well as defining optimal settings for high-intensity focused ultrasound therapy (Carstensen et al., 1980; Cartersen, 1998; Duck and Starritt, 1983; Filonenko and Khokhlova, 2001; Ginter et al., 2002; Goss and Fry, 1981; Jackson et al., 2013; Muir and Cartersen, 1980) and lithotripsy (Cleveland and McAteer, 2007). In addition, tissue harmonic imaging has found wide application, improving the resolution of images with respect to those obtained in fundamental mode (Burns et al., 2000; Ma et al., 2005; Shen and Li, 2001; Zhang and Gong, 2006). Furthermore, stemming from a different underlying mechanism, contrast agents have become a useful tool in the clinic, generating a strong nonlinear signal when isonified and allowing for the extraction of information about vascular perfusion and dispersion (Panfilova et al., 2019; van Sloun et al., 2017).

Apart from the established medical applications of nonlinearity, new ultrasound modalities for the quantification of the parameter of nonlinearity (Madigosky et al., 1981) $B/A$ have been continuously developed for the last few decades in an effort to bring it to the clinic. This parameter characterizes the degree of nonlinearity of a medium. Studies of aqueous solutions have concluded that $B/A$ is influenced by the chemical composition and molecular structure of the solutes (Gong et al., 1993; Sarvazyan et al., 1990; Sehgal et al., 1986a), and were found to be useful to assess the structure of silicone oil used in eye surgery (Zhe et al., 2014). It has also been shown to be useful for tissue characterization, demonstrating distinct values for fatty (Law et al., 1985), malignant, healthy, and cirrhotic tissue in the liver (Errabolu et al., 1993; Sehgal et al., 1984; Sehgal et al., 1986a). Since these different tissue conditions are also associated with different compositions, several papers have developed models defining $B/A$ depending on the constituents of the studied substance (Apfel, 1983; Eversbach et al., 1991), leading to works estimating tissue content from its $B/A$ value combined with additional parameters (e.g., speed of sound, compressibility) (Apfel, 1986; Errabolu et al., 1987; Gong et al., 1993; Sehgal et al., 1986a).

In studies with the same chemical composition, it was shown that $B/A$ increases with structural hierarchy of tissue (e.g., intact liver vs homogenized liver) (Law et al., 1981, 1983; Zhang et al., 1991) and that $B/A$ was sensitive to structural changes in tissue caused by disease (Gong et al., 1993; Zhang and Gong, 1999). Moreover, there have been indications that $B/A$ reflects the quasilattice structure of water, i.e., the ratio of bound to unbound water molecules (Sehgal et al., 1986b; Yoshizumi et al., 1987), altered in malignant tissues (Chung et al., 2008; Nikolaï et al., 1987) and skin disease (Takemuchi et al., 1986).

$B/A$ has also been used to quantify the nonlinear scattering properties of ultrasound contrast agents (Verboven,
From a different perspective, B/A is sensitive to temperature, increasing for most liquids as the temperature increases (Khelladi et al., 2009; Lu et al., 2001) and increasing as tissue is heated (Choi et al., 2011; Jackson et al., 2014; Liu et al., 2008; Lu et al., 2004; Sehgal et al., 1986a). Even though some works show a small B/A increment when tissue is coagulated (Jackson et al., 2014; Saito and Kim, 2011), others state the contrary (Choi et al., 2011; Lu et al., 2004). Several works demonstrated that the B/A profile in tissue follows the temperature profile, generating images of the temperature distribution through B/A (Ichida et al., 1983; Liu et al., 2008; Lu et al., 2004) and suggesting B/A as a tool for high intensity focused ultrasound (HIFU) treatment monitoring (Dongen and Verweij, 2008; Varray et al., 2011b). Besides this, there is evidence that some tumors exhibit an increased temperature compared to surrounding parenchyma (Fear et al., 2002), and that glucose administration is able to raise their temperature by 7°C (Jain et al., 1984), suggesting that the temperature distribution may help to identify tumor location. This body of evidence fortifies the motivation to develop B/A measurement methods, whether it is for assessment of biological liquids or nonlinear imaging aimed at tissue diagnosis or temperature monitoring.

The finite amplitude method (FAM) exploits the dependency of the wave and achieves high-quality retrofocusing. This way, the energy of a nonlinear wave is attenuated to a higher extent than that of a small-signal linear wave. FAMs exploit all these alterations, quantifying distortion through direct observation of the wave profile (Hunter et al., 2016; Mikhailov and Shutilov, 1959; Takahashi, 1995), through harmonic content (Adler and Hiedemann, 1962; Beyer, 1960; Fujii et al., 2004; Gong et al., 1985; Law et al., 1985; Liu et al., 2008; Shkovlovskaya-Kordi, 1963; Varray et al., 2011b; Wallace et al., 2007; Zhang and Gong, 1999; Zhang and Dunn, 1987) or by observing nonlinearly induced attenuation (Byra et al., 2017; Ikata et al., 1980; Kashiwao et al., 1987; Nikoomand and Liu, 1989). This family of methods counts the largest number of publications of all. Even though FAMs are less accurate than the thermodynamic method, they require a much simpler measurement setup and have high potential for a clinical application, enabling B/A tomography for in-transmit measurements and a few echo-mode imaging strategies.

The parametric array method requires transmission of two, typically collinear, beams that generate secondary waves at the sum and difference frequencies. The amplitude of these waves is proportional to the medium B/A (Barrière and Roher, 2001; Bereza et al., 2008; Nakagawa et al., 1984; Zhang et al., 2001a). The secondary beams are narrow, less prone to diﬀraction than those observed with FAM, and do not have side lobes. Parametric array tomography allows for higher resolution, compared to finite amplitude tomography (Gong et al., 2004; Wang et al., 2003). No echo-mode imaging has been performed with this method.

The pump wave method registers the speed of sound change of a low-amplitude high-frequency wave when another high-amplitude low-frequency wave modulates the pressure in the medium (Ichida et al., 1983; Kato and Watanabe, 1994; Sato et al., 1985). Uniquely, this method allows for a reconstruction of the B/A profile along the path of the low-amplitude high-frequency wave from a through-transmission measurement. A particular case of this method, the second order ultrasound field technique (SURF), has been utilized to acquire echo-mode images representing the B/A distribution (Fukukita et al., 1996; Kvam et al., 2019b).

The method of phase conjugated beams (Krutiansky et al., 2007; Preobrazhensky and Pernod, 2003) utilizes a wave phase conjugater to reverse the beam insonating it and radiate its amplified version back to the source. The amplitude of the harmonics of the reradiated beam reflects the B/A of the propagation medium. Phase conjugation provides the unique capability to compensate for phase distortion of the wave and achieves high-quality retrofocusing. Only C-scan images of isoechoic phantom have been acquired with this method. The possibility of echo-mode imaging is excluded.

The vast body of literature devoted to nonlinear ultrasound has already provided material for several review papers. Beyer (1973), Duck (2002), Hamilton and
Blackstock (1998), Muir and Carstensen (1980) discuss the origins of nonlinearity and the way it manifests itself with further consequences in practical applications. Some of these (Beyer, 1973; Hamilton and Blackstock, 1998) introduce separate equations for different states of matter: gas, liquid, and solids. Hamilton and Blackstock (1998) and Naugolnykh (2009) wrote historical reviews on the evolution of nonlinearity in ultrasound. Zheng et al. (1999) wrote a review on material characterization with the help of nonlinear acoustics, devoting a significant portion of it to solids. (Björn, 1986, 2005, 2010; Hamilton and Blackstock, 1998; Zhang and Gong, 2006) are review papers that summarize the progress in B/A measurement methods either over a short time span, devote their attention mainly to a specific measurement strategy, or provide a brief general overview of the main concepts of the existing methods. A concise review of most techniques for B/A measurement has been given by Sato and Yamakoshi more than 30 years ago (Sato and Yamakoshi, 1986). Varray et al. (2011a) presented a review of FAMs that have the potential to be extended to echo-mode regarding the parametric array and pump wave method as one of the above.

This review aims at presenting an extensive and comprehensive up to date overview of B/A measurement and B/A imaging methods of liquids and liquid-like media (e.g., tissue). Importantly, it gives more focus to methods that are relevant for a medical application and discusses the most common pitfalls in this context. By identifying blind spots and limitations we aim at suggesting directions of research that may bring B/A to the clinic. This review paper is further separated into the following sections: Sec. II, theoretical background; Sec. III, Thermodynamic method; Sec. IV, method for aqueous solutions; Sec. V, FAM; Sec. VI, parametric array; Sec. VII, pumping waves; Sec. VIII, phase conjugate beam, and Sec. IX, conclusion.

Section II explains the origin of B/A, presents the most utilized wave equations of nonlinear acoustics, and gives a short overview of the main B/A measurement groups of methods. The sections devoted to various methods (Secs. III–VIII) start with a short introduction of the governing equations and the first published works, followed by the resulting developments, subdivided depending on the adopted measurement strategies. In cases where this has been accomplished, the sections are concluded with studies that presented B/A images. Since the review introduces the basic theory required to understand the physics behind the presented measurement strategies, it is also suited for a reader who is new to nonlinear ultrasound.

II. THEORETICAL BACKGROUND

A. B/A origin

An ultrasound wave consists of a series of compressions and rarefactions. Linear acoustics views density as linearly dependent on pressure. However, this is an approximation, and ultrasound propagation, in general, is a nonlinear process. The adiabatic equation of state expresses the pressure-density relation with the Taylor expansion series (Beyer, 1960; Coppens et al., 1965; Hamilton and Blackstock, 1998),

\[ P = P_0 + \rho_0 \left( \frac{\partial P}{\partial \rho} \right)_{0s} \frac{\rho - \rho_0}{\rho_0} + \frac{\rho_0}{2} \left( \frac{\partial^2 P}{\partial \rho^2} \right)_{0s} \left( \frac{\rho - \rho_0}{\rho_0} \right)^2 + \ldots \]

(1)

Here, \( P \) and \( P_0 \) are instantaneous and hydrostatic pressures, \( \rho \) and \( \rho_0 \) are instantaneous and equilibrium densities of the medium under investigation and the partial derivatives are taken about the equilibrium state (indicated by the subscript 0) and constant entropy (indicated by subscript s). One can define

\[ A = \rho_0 \left( \frac{\partial P}{\partial \rho} \right)_{0s} = \rho_0 c_0^2, \]

(2)

where \( c_0 \) is the small-signal speed of sound, and

\[ B = \rho_0 \left( \frac{\partial^2 P}{\partial \rho^2} \right)_{0s}, \]

(3)

making

\[ \frac{B}{A} = \frac{\rho_0}{c_0^2} \left( \frac{\partial^2 P}{\partial \rho^2} \right)_{0s} = \frac{\rho_0}{c_0^2} \left( \frac{\partial c^2}{\partial \rho} \right)_{0s} = \frac{2 \rho_0 c_0}{(\partial P/\partial \rho)_{0s}}. \]

(4)

The relative importance of second-order nonlinear effects to linear effects can be expressed with the nonlinear parameter \( B/A \) or the alternative nonlinear coefficient (Varray et al., 2011a), expressed as \( \beta = 1 + (B/2A) \) for liquid and liquid-like media (e.g., tissue).

As stated previously (Beyer, 1973; Hamilton and Blackstock, 1998), one may differentiate Eq. (1) by \( \rho \) and, by substituting the speed of sound \( c^2 = (\partial P/\partial \rho)_s \), obtain

\[ \frac{c}{c_0} = 1 + \frac{B}{2A} \left( \frac{\rho - \rho_0}{\rho_0} \right) = 1 + \frac{B}{2A c_0} \]

(5)

for a plane progressive wave, illustrating that the local speed of sound \( c \) is dependent on \( B/A \) and \( u \), the particle velocity. The former is an oscillating disturbance, induced by ultrasound propagation. This explains the origin of accumulating wave distortion, leading to saw-tooth waves: the compressional part of the wave (the high density region, with positive particle velocity and positive excess pressure) travels faster than the rarefractional part, contributing to wave distortion proportionally to \( B/A \).

Tables I and II summarize the measured \( B/A \) values for liquids and animal tissues. As one can see, at atmospheric pressure and room temperature \( B/A \) is in the range of 5–11 for most liquids and liquid-like media.
TABLE I. Liquids. This table presents B/A values of some pure liquids at atmospheric pressure and in a temperature range of 20 °C–30 °C. When several studies are stated, all of them were included in the column “Studies” and only one value was chosen to be stated in the column “B/A.”

<table>
<thead>
<tr>
<th>Medium</th>
<th>B/A</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>5.1</td>
<td>Beyer, 1960; Davies et al., 2000; Zha et al., 1983</td>
</tr>
<tr>
<td>Methanol</td>
<td>9.7</td>
<td>Lu et al., 1998</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>9.9</td>
<td>Zhang and Dunn, 1991</td>
</tr>
<tr>
<td>Ethanol</td>
<td>10.4</td>
<td>Lu et al., 1998</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>8.3</td>
<td>Davies et al., 2000; Zhu et al., 1983</td>
</tr>
<tr>
<td>Glycerol</td>
<td>10.1</td>
<td>Harris et al., 2007; Khelladi et al., 2009; Zeqiri et al., 2015</td>
</tr>
<tr>
<td>Methanol</td>
<td>9.6</td>
<td>Coppens et al., 1965; Lu et al., 1998; Plantier et al., 2002b</td>
</tr>
<tr>
<td>Glycerine</td>
<td>9.4</td>
<td>Mikhailov and Shutilov, 1960</td>
</tr>
<tr>
<td>Corn oil</td>
<td>11.4</td>
<td>Harris et al., 2007; Kujawska et al., 2003</td>
</tr>
<tr>
<td>Linseed oil</td>
<td>9</td>
<td>Kujawska et al., 2003</td>
</tr>
<tr>
<td>Silicone oil</td>
<td>11</td>
<td>Takahashi, 1995</td>
</tr>
<tr>
<td>Olive oil</td>
<td>10.7</td>
<td>Saito and Kim, 2011</td>
</tr>
<tr>
<td>Hyper-branched silicone oil</td>
<td>8.5</td>
<td>Zhe et al., 2014</td>
</tr>
<tr>
<td>Linear silicone oil</td>
<td>9.7</td>
<td>Zhe et al., 2014</td>
</tr>
<tr>
<td>1-propanol</td>
<td>9.5</td>
<td>Banchet et al., 2000</td>
</tr>
<tr>
<td>1-butanol</td>
<td>9.7</td>
<td>Banchet et al., 2000</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>10.4</td>
<td>Akiyama, 2000; Saito, 1993a; Saito et al., 2005</td>
</tr>
<tr>
<td>1-pentanol</td>
<td>10.0</td>
<td>Banchet et al., 2000</td>
</tr>
<tr>
<td>1-hexanol</td>
<td>10.2</td>
<td>Banchet et al., 2000</td>
</tr>
<tr>
<td>1-heptanol</td>
<td>10.6</td>
<td>Banchet et al., 2000</td>
</tr>
<tr>
<td>1-octanol</td>
<td>10.7</td>
<td>Banchet et al., 2000</td>
</tr>
<tr>
<td>1-decanol</td>
<td>10.7</td>
<td>Banchet et al., 2000</td>
</tr>
<tr>
<td>N-butanol</td>
<td>11.2</td>
<td>Lu et al., 1998; Plantier et al., 2002b; Shklovskaya-Kordi, 1963</td>
</tr>
<tr>
<td>1-propanol</td>
<td>10.3</td>
<td>Fukukita et al., 1996</td>
</tr>
<tr>
<td>N-propanol</td>
<td>10.7</td>
<td>Coppens et al., 1965; Lu et al., 1998</td>
</tr>
<tr>
<td>1,2-propanediol</td>
<td>11.5</td>
<td>Zorebski and Zorebski, 2009</td>
</tr>
<tr>
<td>Acetone</td>
<td>9.2</td>
<td>Coppens et al., 1965</td>
</tr>
</tbody>
</table>

B. Main wave equations

To obtain the equations governing the propagation of ultrasound waves in fluid homogeneous media one may refer to the equation of motion, the continuity equation, the heat transfer equation, and the equation of state [Eq. (1)] (Naugolnykh and Ostrovskii, 1998). For an ultrasound wave, together these equations describe the relationship between the spatially varying quantities of pressure, particle velocity, density, as well as heat transfer, related to loss. When these equations model ideal fluid (lossless fluid) and only linear terms are kept, one may derive the well-known wave equation Crocker (1997),

\[
\frac{\partial^2 P(z,t)}{\partial z^2} - \frac{1}{c_0^2}\frac{\partial^2 P(z,t)}{\partial t^2} = 0, \tag{6}
\]

in one-dimensional (1D) space, where we chose to describe the pressure variation \( P \), dependent on the coordinate \( z \) and
TABLE II. (Continued)

<table>
<thead>
<tr>
<th>Medium</th>
<th>B/A</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human whole blood</td>
<td>6.3</td>
<td>Xu et al., 2003</td>
</tr>
<tr>
<td>Bovine serum albumin solutions (various</td>
<td>5.2–7.4</td>
<td>Dunn et al., 1982; Law et al., 1981, 1985; Zha et al., 1983</td>
</tr>
<tr>
<td>Hemoglobin solutions (various</td>
<td>5.2–7.7</td>
<td>Dunn et al., 1982; Law et al., 1981</td>
</tr>
<tr>
<td></td>
<td>Milk</td>
<td>5.1, 5.9</td>
</tr>
<tr>
<td></td>
<td>Egg yolk</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>Egg white</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.2</td>
</tr>
</tbody>
</table>

Time $t$. When second order nonlinear effects are considered [e.g., equation of state given in the form of Eq. (1)] and propagation in three-dimensional (3D) space is addressed, one can obtain the Westervelt equation (Westervelt, 1963),

$$\nabla^2 P - \frac{1}{c_0^2} \frac{\partial^2 P}{\partial t^2} = -\frac{\beta}{\rho_0 c_0^4} \frac{\partial^2 P}{\partial t^2},$$

(7)

where $\nabla^2 = \partial^2 / \partial x^2 + \partial^2 / \partial y^2 + \partial^2 / \partial z^2$ is the Laplacian. The term on the right-hand side of Eq. (7) models cumulative nonlinear effects, while local nonlinear effects are neglected here (Hamilton and Blackstock, 1998; Jeong et al., 2016), implying that the Westervelt equation is valid at propagation distances further than a few wavelengths from the source. Equation (7) models sound propagation of plane waves or quasi-plane waves, like directional beams (Devaney, 1980; Hamilton and Blackstock, 1998) in homogeneous lossless media. It was further expanded to include loss in a weakly thermoviscous fluid (Hamilton and Blackstock, 1998; Naugolnykh and Ostrovskii, 1998; Sapožnikov, 2015; Szabo, 1994b; Tjotta and Tjotta, 1981),

$$\nabla^2 P - \frac{1}{c_0^2} \frac{\partial^2 P}{\partial t^2} = -\frac{\delta}{c_0^2} \frac{\partial^2 P}{\partial t^2} - \frac{\beta}{\rho_0 c_0^4} \frac{\partial^2 P}{\partial t^2},$$

(8)

where $\delta = 2c_0^3 \kappa / \omega^2$ is sound diffusivity, proportional to $\omega$, the attenuation coefficient. Importantly, loss in a weakly thermoviscous fluid assumes attenuation to be proportional to the squared frequency of the wave $f^2$ (Hamilton and Blackstock, 1998; Naugolnykh and Ostrovskii, 1998; Szabo, 1994b; Tjotta and Tjotta, 1981). This is valid for some liquids (e.g., water, certain oils; Chanamai and McClements, 1998; Chavrier et al., 2006; Naugolnykh and Ostrovskii, 1998; Szabo, 1994a); however, most biological media exhibit a nearly linear attenuation-frequency dependence (Cai et al., 1992; Duck, 1990; Goss et al., 1979; Purrington and Norton, 2012). Alternative time-domain equations exist, incorporating arbitrary attenuation (Cai et al., 1992; Szabo, 1994b), more appropriate for, e.g., tissues. No exact analytical solution to the Westervelt equation exists. However, expressions in the form of integrals have been obtained in Jeong et al. (2016) for the case of weak nonlinearity with the help of the Green’s function and when approximating the source pressure as a sum of Gaussian beams (Wen and Breazeale, 1988).

A somewhat simpler description of nonlinearity and attenuation was provided by Zabolotskaya and Khokhlov (1969) and Kuznetsov (1970). Derived from the same original equations as the Westervelt equation, the Khokhlov-Zabolotskaya-Kuznetsov (KZK) equation [Eq. (9)] makes the additional assumption of the parabolic approximation that holds for “acoustic sources which are many wavelengths across and for field points that are not too close to the source or too far off axis” (Jeong et al., 2016),

$$\frac{\partial^2 P}{\partial \tau \partial z} = \frac{\delta}{2c_0^3 \partial \tau^2} + \frac{\beta}{2\rho_0 c_0^4} \frac{\partial^2 P}{\partial \tau^2} + \frac{c_0}{2} \nabla^2 P. \tag{9}$$

Here, $\nabla^2 = \partial^2 / \partial x^2 + \partial^2 / \partial y^2 + \partial^2 / \partial z^2$ is the transverse Laplacian and $\tau$ is the retarded time $\tau = t - (z/c_0)$. The terms on the right side of the equation from left to right represent wave attenuation, nonlinearity, and diffraction effects (Zhao and McGough, 2014). The diffraction effect describes the deviation of the field from a plane wave, due to finite source geometry and is somewhat elaborated on in Sec. VB1. An explicit solution to the KZK equation for the case of weak nonlinearity has been derived in Froyesa (1994), Jeong et al. (2015), and Ji et al. (2011).

The simplest equation describing combined effects of nonlinearity and thermoviscous loss is the Burgers equation (Burgers, 1948),

$$\frac{\partial P}{\partial \tau} - \frac{\beta}{\rho_0 c_0^4} P \frac{\partial P}{\partial \tau} = \frac{\partial^2 P}{2c_0^3 \partial \tau^2}. \tag{10}$$

It considers only plane progressive waves, and therefore, does not account for the diffraction effects. Just as for the Westervelt equation, another form of Eq. (10) can be adopted for biological tissues and liquids, accounting for an arbitrary frequency dependence of attenuation (Blackstock, 1985; Chavrier et al., 2006; Chen and Holm, 2004). The lossless Burger’s equation is derived by setting the attenuation coefficient $\kappa = 0$ (and therefore $\delta = 0$) to zero,

$$\frac{\partial P}{\partial \tau} - \frac{\beta}{\rho_0 c_0^4} P \frac{\partial P}{\partial \tau} = 0. \tag{11}$$

The exact solutions to the lossy and lossless Burger’s equations are known, derived by Fubini-Ghiron (1935) and Keck and Beyer (1960), respectively. These solutions are presented further in this review (Sec. VB). Unlike the Burgers equation, the Westervelt and ZK equations are mainly solved numerically, providing much more accurate predictions of the pressure field (Demi et al., 2011; Doinikov...
et al., 2014; Purrington and Norton, 2012; Zhao et al., 2014). At the same time, solutions of the Burgers equation provide simple formulas for the fundamental and higher harmonic pressures. Diffraction affects can be accounted for in the solutions in a post hoc manner.

III. THERMODYNAMIC METHOD

It has been shown in Eq. (4) that $B/A$ is proportional to the change in sound velocity occurring with an isentropic (adiabatic) change of hydrostatic pressure. The term isentropic refers here to a process where no heat or matter is abstracted or conveyed to the system from outside. Once the derivative in Eq. (4) is expanded, as previously demonstrated (Beyer, 1960; Hamilton and Blackstock, 1998; Rudnick, 1958),

$$\frac{B}{A} = 2\rho_0 c_0 \left( \frac{\partial c}{\partial P} \right)_{T,0} + 2\rho_0 T q \left( \frac{\partial c}{\partial T} \right)_{P,0}. \tag{12}$$

$B/A$ can be expressed through the change in sound velocity caused by isothermal pressure and isobaric temperature ($T$) changes. The parameter $q = (1/V)(\partial V/\partial T)_P$ is the isobaric volume coefficient of thermal expansion and $C_P$ is the specific heat at constant pressure. $B/A$ is sometimes referred to in the literature as the adiabatic nonlinear parameter, while the first term on the right-hand side of Eq. (12) is referred to as the isothermal nonlinear parameter (Errabolu et al., 1988; Varray, 2011) $(B/A)'$,

$$\left( \frac{B}{A} \right)' = 2\rho_0 c_0 \left( \frac{\partial c}{\partial P} \right)_{T,0}. \tag{13}$$

The remaining term in Eq. (12) is referred to as the isobaric nonlinear parameter,

$$\left( \frac{B}{A} \right)'' = 2\rho_0 T q \left( \frac{\partial c}{\partial T} \right)_{P,0}. \tag{14}$$

In general, the thermodynamic methods can be classified into two groups, where $B/A$ is determined either from Eq. (12), as it was initially done, or from Eq. (4). Within these groups, the strategies to measure the speed of sound $c$ differ. All studies carried out with the thermodynamic method require a velocimeter: a vessel of known length $L$, comprising the test liquid and the transmitter-receiver equipment, inserted in a liquid-filled pressure vessel, e.g., water (Law et al., 1983, 1985) or oil (Greenspan and Tschiegg, 1957, 1959; Wilson, 1959) that is in turn submerged in a bath with controlled temperature (Fig. 1).

A. Traditional thermodynamic technique

The traditional thermodynamic technique determines $B/A$ via Eq. (14). The required speed of sound measurement can be performed with different techniques, allowing to infer the travel time (time of flight) $t_{tr}$ of the wave through the velocimeter of known length $L$ (Fig. 1). All the identified works utilizing the traditional thermodynamic technique are summarized in Table III, stating the utilized technique and the parameter directly measured, as well as the specified measurement uncertainty and the investigated media.

The first paper reporting the determination of $B/A$ by the thermodynamic method (Beyer, 1960) used thermodynamic data previously acquired by other scientists (Greenspan and Tschiegg, 1957, 1959; Wilson, 1959) for several liquids. In Greenspan and Tschiegg (1957, 1959) and Wilson (1959), $t_{tr}$ was inferred with the help of a single-circuit (Ficken and Hiedemann, 1956; Zorebski et al., 2005). This circuit allows for triggering of the generator to send a pulse once the preceding pulse is received and, therefore, to infer $t_{tr}$ through the pulse repetition frequency (PRF). In this work, to improve the accuracy of the measurement Greenspan and Tschiegg (1957, 1959) and Wilson (1959) adjusted the PRF of the generator so that a new pulse was transmitted when the echoes of the previously transmitted pulse were superimposed on the receiver. This way, the device allowed determining the speed of sound from the pulse transit time $t_{tr}$, inferred from the PRF and the distance travelled by the pulse ($L$) equal to twice the length of the vessel,

$$c = 2L/t_{tr}. \tag{15}$$

Hagelberg et al. (1967) and Holton et al. (1968) performed the speed of sound $c$ measurement in water with the pulse-echo method: using one transducer as the source and receiver, where $t_{tr}$ was inferred from the interval between echoes reflected from an acoustic mirror positioned at the other end of the vessel.

Law et al. (1983) measured the coefficient of nonlinearity of biological solutions and soft tissues. Since for the studied substances, values of $q$ and $C_P$ in Eq. (12) were not known, the authors used the well-known values for water: the values for tissues measured in former studies showed a difference with water up to 30%, and as previously
discovered, the term \((B/A)^n\) contributed only 3% to the \(B/A\) value. The speed of sound was inferred from a direct measurement of the time of flight based on the display of the oscilloscope, showing the driving and received signals. Law et al. (1985) observed no dependence of \(B/A\) on solute molecular weight in dextran solutions and a linear dependency on solute concentration. The authors postulated that nonlinearity is a result of solute-solvent interactions. The authors also identified that homogenization of tissue reduced \(B/A\) and, in general, \(B/A\) showed an increasing trend with the specimen’s structural hierarchy. It is worth mentioning that this paper presents a comprehensive diagram and description of the apparatus used.

Zorebski and Zorebski (2009) utilized the pulse-echo-overlap method (Greenspan and Tschiegg, 1957; Zorebski et al., 2005) to determine the speed of sound in lower alkanediols by extracting the PRF at conditions of overlapping echoes coming back from a reflector. The authors acquired \(B/A\) at pressures up to 100 MPa and temperatures from 21 to 46 °C. Zorebski et al. (2016) extended the range of studied temperatures, measuring \(B/A\) from 16 to 46 °C.

The accuracy of the traditional thermodynamic techniques, taking into account further measurement uncertainties (e.g., temperature and pressure), resulted in a global uncertainty of the \(B/A\) estimation within 3% for liquid and 5% for tissue (Table III). The higher uncertainty for tissue samples accounts for the inhomogeneous speed of sound (Law et al., 1985). The studies conducted with the traditional thermodynamic method revealed that \(B/A^n\) is much smaller compared to \(B/A'\) (constituting less than 5% for fluorocarbon fluids (Madigosky et al., 1981), 9% of \(B/A\) for the liquids studied in Zorebski and Zorebski (2009), and 12% of the pressure-dependent term for methanol-water mixtures (Coppens et al., 1965)). Besides this, \(B/A'\) has shown to be always positive, while \(B/A^n\) can exhibit positive and negative values depending on the studied material. Hagelberg et al. (1967) and Holton et al. (1968) illustrated that for a range of temperatures up to 80 °C and a very wide range of pressures \(B/A\) of water has small variability (from 4.1 to 6.8), and increases monotonically with temperature for a pressure value of 1 atm. Coppens et al. (1965) demonstrated that \(B/A\) of alcohol mixtures show low variability with temperature. Madigosky et al. (1981) reported fluorocarbon fluids to have the highest nonlinearity reported so far (\(B/A = 13\)). Law et al. (1983, 1985) demonstrated the dependence of \(B/A\) on the chemical composition of biological solutions as well as the structural hierarchy of biological material.

### B. Isentropic thermodynamic technique

The isentropic thermodynamic technique, also referred to as the improved thermodynamic method (Gong et al., 1989; Lu et al., 1998; Plantier et al., 2002a), makes use of Eq. (4) rather than Eq. (12). It requires a rapid (1–3 s) change of pressure to eliminate significant heat transfer with the test vessel. This way, the pressure change can be regarded as an isentropic process. As noted by Zhu et al. (1983), this technique is simpler than its predecessor, since it eliminates the need for measurements at different temperature points. Moreover, as Sehgal et al. (1984) indicated, the traditional thermodynamic method requires knowledge of \(q\) and \(C_p\), which are “not known with great precision for most soft tissues.” The uncertainty of the early isentropic phase method is estimated to be 4% (Everbach and Apfel, 1995).

However, the development of this method is connected to the improvement in the techniques measuring the speed of sound, permitting to reduce the uncertainty to <1% (Table IV). It is velocity measurement techniques that account for the variability of the isentropic phase methods. Therefore, the following section is divided into subsections according to the measured parameter through which the speed of sound is inferred, that being phase \(\phi\), voltage \(U_p\), frequency \(f\), or the time of flight \(t_r\) of a pulse. A summary of the identified works, utilizing the isentropic thermodynamic technique, is presented in Table IV.

The most frequently used are phase measurement techniques, providing more accurate speed of sound estimations compared to earlier methods used in the framework of the traditional thermodynamic technique (Table III). A few others, deriving speed of sound from frequency information, or estimating the time of flight of a pulse, are also used. A detailed explanation follows below.

#### 1. Phase measurements

Among the first publications using the isentropic thermodynamic technique are Emery et al. (1979) and

---

**Table III. Summary of works that measured \(B/A\) with the traditional thermodynamic technique.** The indicators liquid and tissue refer to measurement uncertainties for liquids and tissues, respectively. Uncertainty (Uncert. %) is stated in percent of the measured values.

<table>
<thead>
<tr>
<th>Study</th>
<th>Measured parameter</th>
<th>Uncert. %</th>
<th>Investigated media</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coppens et al., 1965</td>
<td>PRF, sing-around circuit</td>
<td>&lt;3 (liquid)</td>
<td>Organic liquids, water-alcohol mixtures</td>
</tr>
<tr>
<td>Hagelberg et al., 1967; Holton et al., 1968</td>
<td>(t_r), pulse-echo m.</td>
<td>—</td>
<td>Water</td>
</tr>
<tr>
<td>Madigosky et al., 1981</td>
<td>PRF, sing-around circuit</td>
<td>—</td>
<td>Fluorocarbon fluids</td>
</tr>
<tr>
<td>Law et al., 1983</td>
<td>(t_r)</td>
<td>3 (liquid), 5 (tissue)</td>
<td>Biological solutions, soft tissues</td>
</tr>
<tr>
<td>Law et al., 1985</td>
<td>(t_r)</td>
<td>3 (liquid), 5 (tissue)</td>
<td>Biological solutions, soft tissues</td>
</tr>
<tr>
<td>Zorebski and Zorebski, 2009</td>
<td>(t_r), pulse-echo-overlap m.</td>
<td>3 (liquid)</td>
<td>Lower alkanediols</td>
</tr>
<tr>
<td>Zorebski et al., 2016</td>
<td>PRF, sing-around circuit, pulse-echo-overlap m.</td>
<td>3 (liquid)</td>
<td>Ionic liquid</td>
</tr>
</tbody>
</table>
Zhu et al. (1983), measuring $B/A$ of liquids. The authors considered the measurement isentropic, as the applied pressure changes were small (varying from 1 to 2 atm) and too fast ($\approx 2.0$ s) for a significant heat exchange. The speed of sound change is connected to the wave’s transit time $t_r$, and the distance between transducers $L$ via Eq. (16) (Zhu et al., 1983),

$$\frac{\partial \phi}{\partial P} = -\frac{L}{t_r^2} \frac{\partial t_r}{\partial P}. \quad (16)$$

Equation (16) allows us to determine $B/A$ based on Eq. (4) as

$$\frac{B}{A} = -\frac{2\rho_0 c_0^2}{t_r} \left( \frac{\Delta t_r}{\Delta P} \right). \quad (17)$$

To detect the change in transit time $t_r$, Zhu et al. (1983) chose to conduct phase measurements: they compared the phase of the received tone burst to that of a reference signal with a phase mixer and acquired $\Delta t_r$ with the help of a delay line. Since $\Delta \phi = \omega \Delta t_r$ and $t_r = L/c_0$, $B/A$ was determined according to

$$\frac{B}{A} = -\frac{2\rho_0 c_0^3}{\omega L} \left( \frac{\Delta \phi}{\Delta P} \right), \quad (18)$$

where $L$ is the length of the ultrasound path through the liquid. Equation (16) forms the basis of all phase measurement techniques, which in general produced more accurate results compared to earlier strategies. A follow-up paper (Gong et al., 1989) of one of the authors of Zhu et al. (1983) used the same version of the method to measure $B/A$ of biological solutions and soft tissues. Gong et al. (1989) confirmed the results obtained by Law et al. (1985) for homogenized liver versus whole liver, as well as biological solutions, observing that $B/A$ increases with the structural hierarchy of the specimen.

### Table IV. Summary of strategies to measure $B/A$ with the isentropic thermodynamic technique. The uncertainty ($\text{Uncert.}$, %) of the $B/A$ measurement is stated in percent of the measured value for tissues and liquids.

<table>
<thead>
<tr>
<th>Measured parameter</th>
<th>Studies</th>
<th>Uncert., %</th>
<th>Investigated media</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase $\phi$</td>
<td>Zhu et al., 1983</td>
<td>2.5 (liquid)</td>
<td>Liquids, e.g., water, bovine serum albumin solution</td>
</tr>
<tr>
<td></td>
<td>Gong et al., 1989</td>
<td>4 (liquid), 7 (tissue)</td>
<td>Biological solutions and soft tissues</td>
</tr>
<tr>
<td></td>
<td>Sehgal et al., 1984; Sehgal et al., 1986a</td>
<td>3 (tissue)</td>
<td>Normal and malignant human tissues</td>
</tr>
<tr>
<td></td>
<td>Sehgal et al., 1986b</td>
<td>1 (liquid)</td>
<td>Monohydric alcohol-water solutions</td>
</tr>
<tr>
<td></td>
<td>Errabolu et al., 1987</td>
<td>-</td>
<td>Livers, fat, e.g., oils</td>
</tr>
<tr>
<td></td>
<td>Errabolu et al., 1988</td>
<td>3</td>
<td>Human and animal fats, simple mixtures (e.g., skim milk)</td>
</tr>
<tr>
<td>Voltage $\Delta U_p$</td>
<td>Lu et al., 1998</td>
<td>2.2 (liquid)</td>
<td>Water, organic liquids</td>
</tr>
<tr>
<td></td>
<td>Plantier et al., 2002a</td>
<td>2 (liquid)</td>
<td>Water</td>
</tr>
<tr>
<td></td>
<td>Plantier et al., 2002b</td>
<td>2 (liquid)</td>
<td>Primary alcohols</td>
</tr>
<tr>
<td></td>
<td>Plantier et al., 2003</td>
<td>&lt;2.2 (liquid)</td>
<td>Alkanes</td>
</tr>
<tr>
<td></td>
<td>Khelladi et al., 2009</td>
<td>2 (liquid)</td>
<td>Glycerol</td>
</tr>
<tr>
<td></td>
<td>Zhu et al., 2014</td>
<td>&lt;2 (liquid)</td>
<td>Silicone oils</td>
</tr>
<tr>
<td>Transmit time $\Delta t_r$</td>
<td>Zhang and Dunn, 1991</td>
<td>0.7 (liquid)</td>
<td>Water, dextrose, ethylene glycol</td>
</tr>
<tr>
<td></td>
<td>Zhang et al., 1991</td>
<td>Tissues not assessed separately</td>
<td>Cat and rat livers, liver suspensions</td>
</tr>
<tr>
<td>Frequency $f$</td>
<td>Everbach and Apfel, 1995</td>
<td>0.85 (liquid)</td>
<td>Aqueous buffers, protein solutions, lipid oils, emulsions</td>
</tr>
<tr>
<td></td>
<td>Davies et al., 2000</td>
<td>1 (liquid)</td>
<td>Liquids</td>
</tr>
</tbody>
</table>

#### a. Pressure-jump method. Sehgal et al. (1984) presented the pressure jump method. During the pressure increase, the phase of the received signal was monitored. The speed of sound was inferred from Eq. (18). After the pressure change, the system was allowed to equilibrate to the ambient temperature and the authors could also measure the isothermal nonlinear parameter ($B/A$). Sehgal et al. (1984) and Sehgal et al. (1986a) used the method described above, transmitting ultrasound in continuous-wave mode. This configuration was “most suitable for attenuating media” (Sehgal et al., 1984) as tissue since high attenuation avoided the formation of standing waves. Sehgal et al. (1984) measured $B/A$ of several human tissues. They demonstrated that fatty breast tissue had a substantially higher value than parenchymal liver tissue, and that multiple myeloma had a substantially lower $B/A$ compared to normal parenchymal liver tissue. Sehgal et al. (1986a) showed that $B/A$ of fatty liver is higher compared to normal, while cirrhotic and tumorous $B/A$ is lower than for normal liver. Sehgal et al. (1984) and (1986a) are the only papers, to the best of our knowledge, reporting $B/A$ for malignant tissues.

In Errabolu et al. (1987), Errabolu et al. (1988), and Sehgal et al. (1986b), the adiabatic nonlinear parameter and the isothermal nonlinear parameter were measured with the pressure-jump method, detecting the phase change [Eq. (18)] of a shock-excited pulse. Sehgal et al. (1986b) reported $B/A$ of alcohol-water mixtures. Since alcohols have smaller speed of sound and larger $B/A$, their addition to water was expected to increase $B/A$. This was not the case for low concentrations of alcohol. Such an effect on $B/A$ was attributed to the effects of solvent-solute interactions, and alteration in the water-molecule structure due to the addition of alcohol. The authors speculated that, since tissue is composed of 60%–80% of water, changes in the state of tissue due to the change in unbound-bound water ratio must have been reflected in its $B/A$, creating another opportunity for determining tissue properties based on $B/A$. Errabolu...
et al. (1988) demonstrated that human and animal fat tissues are highly nonlinear, with \( B/A \) values ranging between 10 and 12. Moreover, in the range of temperatures from 20 to 37°C, \( B/A \) vs temperature exhibits a positive or flat trend. Errabolu et al. (1987) proposed a two-component model (fat and nonfat), able to predict the fat percentage based on the measured \( B/A \) and speed of sound. The model was tested for livers, fats, oil, and egg mixtures.

b. Phase derivation from output voltage. Lu et al. (1998) utilized a highly sensitive phase comparison technique by transmitting a tone burst signal and producing small pressure changes below 2 atm to liquids. This technique (like Zhu et al., 1983) also utilizes a phase mixer. However, different from other methods, the phase change is inferred from the amplitude of the phase detector rather than with a delay line. The measurements are done for small phase changes (below \( \pi/20 \)), where the output voltage of the phase detector (mixer) \( U_p \) is linearly dependent on signal phase \( \phi \). Therefore, the phase change of the detector signal, \( \Delta U_p \), can be described through the phase change \( \Delta \phi \) as

\[
\Delta U_p = kA_1A_2\Delta \phi, \tag{19}
\]

where \( A_1 \) and \( A_2 \) are the amplitudes of the received and the reference signal that are mixed in the phase detector, and \( k \) is a constant characterizing the phase detector. This way, \( \Delta U_p \) can be utilized to estimate \( B/A \) as

\[
\frac{B}{A} = -\frac{2\rho_0c_0^3}{c_L} kA_1A_2 \left( \frac{\Delta U_p}{\Delta \phi} \right), \tag{20}
\]

The maximum pressure change was adjusted to maintain a linear relation between voltage and phase. Lu et al. (1998) report the technique to have an uncertainty of 2.2%.

This strategy was used to measure \( B/A \) of several liquids (Khelladi et al., 2009; Lu et al., 1998; Plantier et al., 2002a,b; Zhe et al., 2014). A few of these studies (Khelladi et al., 2009; Plantier et al., 2002a,b, 2003) enabled \( B/A \) measurement at pressures up to 100 MPa and temperatures up to 100°C.

2. Transmit time

Zhang and Dunn (1991) developed an isentropic thermodynamic method capable of measuring \( B/A \) of 4-mL sample volumes. This system is important for situations when samples are products of biochemical reactions with small yields or pathological tissue areas which may be of limited locus/size. The distance between the source and receiver in the velocimeter was only 1 cm. The speed of sound was determined with Eq. (17) by calculating the time delay from cross correlation of the transmitted and received pulses. Since the receiver was in the near field, an error was introduced in the velocity measurements; however, the authors stated that their system was nevertheless able to measure within an error of 0.7%, confirmed by measurement of three mixtures.

Zhang et al. (1991) used the above described setup (Zhang and Dunn, 1991) to determine the influence of structural parameters on \( B/A \). Performing measurements of cat and rat liver tissue as well as suspensions acquired from these livers, the authors altered their structure physically and biochemically, and reached the conclusion that structural dependence of \( B/A \) “exists at all three levels of biological structure, viz., the tissue level, the cellular level and the molecular level. The relative contributions due to structural features is 26% at the tissue level, 20% at the cellular level, and 15% at the macromolecular level.”

3. Frequency measurement

Everbach and Apfel (1995) automated the measurement of speed of sound, allowing for the performance of thousands of acquisitions on a sample in a reasonable time. The utilized interferometer consisted of a receiving and source transducer. A phase-locked loop circuit was used to correct for the frequency of the transmitted pulse by \( \Delta f \) so that a constant phase relationship was kept at the receiver transducer as the speed of sound changed in the medium. Since \( \Delta f \) required to keep the phase constant can be defined by

\[
\Delta f/f_0 = \frac{\Delta c}{c_0}, \tag{21}
\]

\( B/A \) can be expressed as

\[
\frac{B}{A} = 2\rho_0c_0^2 \frac{\Delta f}{f_0 \Delta P}, \tag{22}
\]

where \( f_0 \) and \( \rho_0 \) are the initial frequency and density. A pressure of 180 kPa (1.85 atm) was generated in the measurement cell and then released. During this release (3 s) the source transducer transmitted 20-cycle tone bursts at 11 frequencies. Contrary to Sehgal et al. (1984) and Sehgal et al. (1986a), attenuation was an undesired effect for an interferometer, as the measurements were performed for a range of organic and aqueous solutions. The presented method is reported to have an accuracy of about 1%.

Davies et al. (2000) also measured the change in frequency associated with the pressure change [Eq. (22)]. Contrary to Everbach and Apfel (1995), they performed continuous wave phase locking since the continuous wave approach avoids the uncertainty of pulse onset identification. As the system was developed for small-volume samples, the authors encountered near-field problems (Zhang and Dunn, 1991) in an early setup when using phase locking in double-disk interferometers. To overcome this problem, they utilized a cylindrical piezoelectric cavity resonator which, coupled with the developed electronic system, “provided a real-time measurement of the change in speed of sound as function of frequency.” The authors applied a 2-s pressure sweep from 0 to 200 kPa during which 100 data frequencies \( f = f_0 + \Delta f \) were acquired. This system was reported to produce uncertainty of less than 1% for \( B/A \).
IV. METHOD FOR AQUEOUS SOLUTIONS

Sarvazyan et al. (1990) noted that the $B/A$ errors were too large to study solute-solvent mixtures with a small amount of solvent. Most biological compounds cannot be diluted in high concentrations in aqueous solutions due to the low solubility. The $B/A$ change in the possible range of concentration is estimated to be approximately 1% (Sarvazyan et al., 1990), within the error span of the most accurate thermodynamic techniques (see Tables III and IV). For this reason, Sarvazyan et al. (1990) developed a differential method that rather than measuring absolute values, estimated the differences between the solute and the solution, which is a common approach in chemical relaxation kinetics (Eggers and Funck, 1973). The accuracy of the relative measurements of the nonlinearity parameter achieved by this method was 0.3%.

The theory was derived by differentiating Eq. (12) for the traditional thermodynamic method, resulting in the following expression:

$$\frac{\Delta B/A}{C} = \frac{1}{2\rho_0c_0} \left( \frac{\partial c}{\partial P} \right)_T + \left( \frac{\partial \rho}{\partial P} \right)_T \rho_0$$

$$+ \frac{\gamma_0T_0}{\rho_0C_p} \left( \frac{\partial c}{\partial T} \right)_p + \left( [c] + [\gamma] - [C_p] \right)$$

$$\times \left( \frac{\partial c}{\partial T} \right)_p,$$

where capital $C$ is the solute concentration, values attributed to the solvent are denoted by subscript 0, and $\Delta$ refers to the difference between the solution and the solvent for the corresponding expressions. $[c]$, $[\rho]$, $[\gamma]$, $[C_p]$ are relative specific increments of speed of sound, solution density, thermal expansion coefficient, and heat capacity at constant pressure, respectively,

$$[c] = \frac{\Delta c}{c_0C}, \quad [\rho] = \frac{\Delta \rho}{\rho_0C}, \quad [\gamma] = \frac{\Delta \gamma}{\gamma_0C}, \quad [C_p] = \frac{\Delta C_p}{C_pC}.$$  

(24)

Parameters $[\rho]$, $[\gamma]$, $[C_p]$ are known from literature, leaving $[c]$, $\Delta(\partial c/\partial P)_T$, and $\Delta(\partial c/\partial T)_p$ as the values to be measured, given that the solvent parameters with subscript 0 are known.

The setup used in Sarvazyan (1982) is typical for the thermodynamic method (Sec. III). However, several important modifications were made. The measurement cell was represented by a four-channel resonator cell, each with a volume as small as 0.2 mL, all filled with the test liquids. Simultaneous velocity measurements in these chambers were made by the resonator method with an acoustic interferometer. Standing waves form in the cells at resonance frequencies at which the distance between transducers is equal to a whole number of half-wavelengths. This results in amplitude peaks at these frequencies (amplitude frequency characteristic), as well as a particular phase dependence of the received signal on the frequency (phase-frequency characteristic). The authors inferred $\Delta c$ from the phase frequency characteristic, identifying the shift in resonance frequency $\Delta f$ to keep the phase constant at its inflection point [Eq. (21)]. The resonator method is the only technique that can be applied for such small-volume samples (Sarvazyan, 1991). Different from previous thermodynamic studies (Sec. III), the authors introduced a reference cell with the solvent, placed in the same thermostated volume as the solution. This lowered the requirement for the temperature stability of the system.

The above work was employed to assess the acoustic properties of solutions of amino acids and proteins, giving insight into the molecular origins of $B/A$. For instance, the authors discovered that an increase in the number of charged groups that favor bonds with water molecules augments $B/A$, while $\text{CH}_2$ groups decrease it due to decreased accessibly of water to such molecules. The authors also noted a strong sensitivity of $B/A$ to a replacement of a single atomic group within a molecule, compared to ultrasound velocity and density. These observations demonstrated that $B/A$ may be a useful indicator of molecular structure and hydration of biomolecules in solutions. This method enables measurement of the smallest amounts of sample reported and provides the highest measurement accuracy (0.3%) reported until now (Sec. IX, Table VIII). A follow-up paper studied temperature dependencies of $B/A$ of aqueous amino acid solutions (Chalikian et al., 1992).

V. FAM

As demonstrated in Sec. II, the speed of an ultrasound wave at a point in space and time is dependent on $B/A$ (or $B$) and the excess density (or particle velocity) at that point and time. Due to this, as the wave propagates it distorts, which was shown to be equivalent to the generation of higher harmonics (integers of the transmitted frequency) in the frequency domain (Fubini-Ghorn, 1935; Keck and Beyer, 1960; Krasilnikov et al., 1957). As higher harmonics grow, the fundamental component is depleted due to the energy transfer from the fundamental harmonic to the higher harmonics.

All FAMs register the wave after a certain propagation distance in a medium (e.g., Fig. 2) and derive $B/A$ from cumulative nonlinear effects observed in the registered signal. The FAMs can be classified into three main groups: deriving $B/A$ directly from the wave’s shape, from the second harmonic component, and from the fundamental component. A detailed description of each family of methods follows below. The theory presented in the introductory

![FIG. 2. (Color online) Schematic of the most common through-transmission setup used to measure $B/A$ with many FAMs. Here, L is the path in the studied medium. In reflection-mode imaging, the receiver is substituted by a reflector plate, and the source transducer acts as the receiver.](https://doi.org/10.1121/10.0003627)
sections (Secs. VC1 and VB1) of the FAM groups concern only weak nonlinearity (the shock parameter $\sigma = [2\pi f P_1(0)z\beta/\rho_0 C_0^3] \leq 1$), since the pressure amplitudes that demonstrate strong nonlinearity are above the safety regulations for assessment of biological media. Table V, presented below, summarized all the identified FAM works and the utilized strategies to measure $B/A$.

A. Wave shape

1. Light diffraction method

The earliest works observing the wave shape to infer $B/A$ were performed with optical methods (Fig. 3). When an optical wave propagates in a direction perpendicular to the ultrasonic beam, the initially flat wave front of the optical wave is modulated in phase according to the velocity profile of the US wave, possibly distorted due to nonlinear propagation.

This way, measurement of the diffraction of light allows for the reconstruction of the US wave’s velocity profile and quantification of distortion by extracting $w_0$ or $w_1$ from its shape (Fig. 4), and thereby derivation of $B/A$.

This method was implemented by Mikhailov and Shutilov (1960) and Shutilov (1959) and yielded $B/A$ for water and several other optically transparent liquids. More recently, Takahashi (1995) also utilized the waveshape to quantify $B/A$ through the assessment of $w_0$ or $w_1$. In this case, the signal was received with a hydrophone, while the source pressure was determined from the diffraction pattern of light emitted by a laser. This way, the setup was a hybrid of those presented in Figs. 2 and 3. Other works are also known (Nomoto and Negishi, 1965), using the diffraction of light to capture the nonlinear distortion of ultrasound waves and extract $B/A$.

2. Modelling of the wave profile

Chavrier et al. (2006), Hunter et al. (2016), Jackson et al. (2014), and Jeong et al. (2016) utilized the setup presented in Fig. 2, where the signal passed through a medium of length $L$ and was received by a hydrophone or a transducer. Chavrier et al. (2006), Hunter et al. (2016), and Jackson et al. (2014) fit nonlinear waveforms of the received pulses with the Burger’s equation, where $B/A$ (and $z$) was the fit parameter. These works use large source transducers (e.g., 10 cm in diameter; see Jackson et al., 2014) to avoid edge diffraction effects, eliminating the need for diffraction correction and justifying the use of the Burger’s equation which cannot account for diffraction. Conversely, Jeong et al. (2016) developed multi-Gaussian beam models based on a quasilinear approximation of the Westervelt equation and the KZK equation (Jeong et al., 2015), including both diffraction and attenuation effects. This allowed describing the pressure fields of the fundamental and 2nd harmonic with no restrictions for the source size or the distance range. From a single measurement set at distances from 2 to 20 cm, the authors extracted the attenuation coefficients at the fundamental $z_1$ and 2nd harmonic frequency $z_2$, as well as the $\beta$ value by fitting a model to the observed pressure profiles.

A calibration procedure for $P_1(0)$ was required. Works inferring $B/A$ through the wave profile require broadband receivers, able to capture the wave shape accurately.

B. Second harmonic measurements

1. Basic theory

The amplitudes of the higher harmonics in the preshock region ($\sigma \leq 1$) of a plane wave in a lossless medium are given by Fox and Rock (1941), Fubini-Ghiron (1935), and Hamilton and Blackstock (1998).

$$P_n(\sigma) = \left[\frac{2P_1(0)}{n\sigma}\right] J_n(n\sigma),$$

where $n$ is a positive integer indicating the number of the harmonic: the fundamental $P_1(0)$ at the source and higher harmonics $P_{2,3,\ldots}$; and $\sigma$ is the shock parameter $\sigma = 2\pi f P_1(0)z\beta/\rho_0 C_0^3$. Equation (25) is the Fubini solution (Fubini-Ghiron, 1935) of the lossless Burgers equation [Eq. (11)]. By expanding the Bessel function as a power series and neglecting the high order terms, the amplitude of the 2nd harmonic can be expressed as

$$P_2(z) = \left(\frac{B}{A} + 2\frac{\pi z P_1^2(0)}{2\rho_0 C_0^3}\right).$$

This equation illustrates that the amplitude of the 2nd harmonic increases proportionally to $B/A$, to the distance $z$ from the source, and the frequency of the transmitted signal $f$. It also shows a quadratic dependence on the transmitted pressure amplitude $P_1(0)$ at the source.

Later, this theory was further developed to include losses in two alternative ways. The first one was based on the assumption that the attenuation of the fundamental and higher harmonics is independent of each other. Furthermore, the change of the 2nd harmonic amplitude was ascribed to its harmonic generation due to nonzero $B/A$ value and its small-signal absorption (neglecting energy transfer to higher harmonic components) (Thuras et al., 1935). The following expression is the solution to the equation describing the change of the 2nd harmonic:

$$P_2(z) = \left(\frac{2 + B/A}{2\rho_0 C_0^3}\right) P_1^2(0) e^{-z_1^2 - z_2^2} e^{-z_2},$$

where $z_1$ and $z_2$ are the attenuation coefficients of the fundamental and its harmonic. Here, no assumption about the frequency dependence of attenuation has been made, therefore, the formula is valid for liquids and tissues. This expression can be further simplified (Dunn et al., 1982) when assuming $(z_2 - 2z_1)z$ to be small,

$$P_2(z) = \left(\frac{2 + B/A}{2\rho_0 C_0^3}\right) P_1^2(0) e^{-(z_1 + (z_2/2))z},$$

The previous simplification leads to an error of 1% when the value $(z_2 - 2z_1)z$ is $< 1/2$ (Dunn et al., 1982). Equation (28)
TABLE V. Intercomparison of FAMs. The table discusses the main principle, advantages and disadvantages, and accuracy of FAM variations in their initial form, developed for $B/A$ estimation as a global parameter. In the column Uncert., %, the measurement error is stated for liquids, tissues, or phantoms (tissue-mimicking or layers of liquid), respectively. The column Images states whether or not any experimental works presented $B/A$ images, therefore, visualizing $B/A$ distribution rather than a single global $B/A$ value. $P_1(0)$, source pressure; $P_2$, 2nd harmonic pressure.

<table>
<thead>
<tr>
<th>Main Groups</th>
<th>Subgroup</th>
<th>Main principle</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Uncert., %</th>
<th>Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wave shape</td>
<td>Light diffraction. Sec. V A 1</td>
<td>Assessment US wave shape through diffraction of light</td>
<td>- Accurate, - No per se assumptions about the harmonic content of the signal is needed</td>
<td>- Complicated setup that includes a laser and an optical receiving system</td>
<td>7–8 (liquid) (Mikhailov and Shutklov, 1960)</td>
<td>—</td>
</tr>
<tr>
<td>Modelling of the wave profile. Sec. V A 2</td>
<td>Fit pulse waveforms to nonlinear models</td>
<td>- No per se assumptions about the harmonic content of the signal is needed</td>
<td>- Requires $P_1(0)$ (calibration) - Broadband receiver needed</td>
<td>&lt;8 (liquid) (Kashkooli et al., 1987)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Second harmonic measurement</td>
<td>2nd harmonic maximum. Sec. V B 2 a</td>
<td>Experimentally identifying the distance from the source of $P_2$ maximum</td>
<td>- No clear advantages identified - Measurements at several distances</td>
<td>- Only for viscous liquids - Measurements at several distances</td>
<td>10 (liquid, tissue) (Chavrier et al., 2006; Hunter et al., 2016; Jackson et al., 2014), 5 (liquid) (Jeong et al., 2016)</td>
<td>—</td>
</tr>
<tr>
<td>Second harmonic measurement</td>
<td>Extrapolation scheme. Sec. V B 2 b</td>
<td>Extrapolating $P_2(a)/P_1(0)$ to zero distance from the source</td>
<td>- Does not need any attenuation measurement</td>
<td>- Requires transducer calibration to estimate $P_1(0)$ - Measurements at several distances</td>
<td>10 (liquid) (Adler and Hiedemann, 1962), 8 (liquid, tissue) (Law et al., 1985), 2–11 (liquid) (Wallace et al., 2007), 10 (liquid) (Law et al., 1981; Dunn et al., 1982)</td>
<td>—</td>
</tr>
<tr>
<td>Single measurement. Sec. V B 2 c</td>
<td>Measuring the 2nd harmonic amplitude at a distance</td>
<td>- One measurement at one distance is sufficient for $B/A$ estimation - Requires measurements at only one distance</td>
<td>- Requires transducer calibration to estimate $P_1(0)$ and an extra $P_2$ measurement - Requires transducer calibration to estimate $P_1(0)$, $z$ (unless can be neglected)</td>
<td>4 (liquid) (Cobb, 1983), &lt;8 (tissue) (Zhang and Dunn, 1987), 7.5 (liquid) (Chitnahla et al., 2007), 3 (liquid) (Pantea et al., 2013), 12 (liquid) (Panfilova et al., 2018)</td>
<td>Echo-mode: (van Sloun et al., 2015)</td>
<td></td>
</tr>
<tr>
<td>Source $P_1(0)$-$P_2$ characteristic. Sec. V B 2 d</td>
<td>Fitting a line to $P_2$ depending on the source pressure</td>
<td>- Requires measurements at only one distance</td>
<td>- Source pressure in the studied medium may be altered, compared to the reference medium (due to different acoustic impedances of the media)</td>
<td>4 (liquid) (Gong et al., 2014), &lt;8 (liquid) (Gong et al., 1984), 3 (liquid) (Zhang et al., 1991), &lt;3 (tissue) (Yu et al., 2014), 8 (liquid) (Gong et al., 1999)</td>
<td>Echo-mode: (Toulemonde et al., 2015; Varray et al., 2011b)</td>
<td></td>
</tr>
<tr>
<td>Second harmonic measurement</td>
<td>Comparative method. Sec. V B 2 e</td>
<td>Comparing $P_2$ in the sample to that in a reference medium at a fixed distance from the source</td>
<td>- Requires measurements at only one distance - No source calibration needed - Potential to mitigate diffraction effects as for the comparative method</td>
<td>- Requires little sample volume - Source pressure in the studied medium may be altered, compared to the reference medium (due to different acoustic impedances of the media)</td>
<td>8 (liquid) (Gong et al., 1984), &lt;8 (liquid, phantom) (Dong et al., 1999), &lt;10 (liquid) (Harris et al., 2007), &lt;5 (tissue, liquid) (Kujawksa et al., 2003)</td>
<td>Tomography: (Zhang et al., 1996), (Zhang and Gong, 1999), reflection tomography and echo-mode C-scans: (Gong et al., 2004)</td>
</tr>
<tr>
<td>FAIS. Sec. V B 2 f</td>
<td>Extracting $\beta$ from the ratio $P_2/P_1$ (with the sample in the path between the source and the receiver and without)</td>
<td>- As for the comparative method</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>Second harmonic measurement</td>
<td>Transmission line method. Sec. V B 2 g</td>
<td>Measuring the fundamental saturation as source pressure is increased</td>
<td>- No transducer calibration required - Acquisitions at several source-receiver separation distances</td>
<td>20 (liquid) (Kushibiki et al., 1997), &lt;2 (liquid) (Dong et al., 2006)</td>
<td>—</td>
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</table>
is particularly applicable to tissue since tissue attenuation exhibits a nearly linear frequency dependence (Duck, 1990; Goss et al., 1979).

An alternative way to take attenuation into account was proposed (Blackstock, 1966; Keck and Beyer, 1960) when solving the Burger’s equation [Eq. (10)] for the weakly nonlinear case characterized by a Goldberg number

\[ G = \frac{2\pi P_0 \beta}{\rho_0 c_0^2} \alpha < 1 \]

(Hamilton and Blackstock, 1998),

\[ P_2(z) = \left( \frac{B}{A} + 2 \right) \frac{\pi P_1^2(0)}{2x_i e_0 c_0} \left( e^{-2xz} - e^{-4xz} \right), \tag{29} \]

where \( \alpha \) is the attenuation coefficient of the fundamental wave. The Goldberg number reflects the balance between the nonlinear processes and the absorption processes (Duck, 2002). Equation (29) applies to weakly thermoviscous fluids (Sec. II B).

The theory above, as already mentioned, was developed for plane waves. Due to this, most studies use a plane piston source as a signal transmitter and perform the measurements in the near field at distances closer than the Rayleigh distance \( F_d \) (\( F_d = \pi r^2 / \lambda \), where \( r \) is the source radius and \( \lambda \) is the signal wavelength; Kuntz et al., 1983). In reality, however, even the near field of a plane piston source differs from an ideal plane wave, due to interference of signals originated from different locations of the source (Huygens principle). These effects are diffraction effects (Duck, 2002) and result in a complicated diffraction pattern of pressure amplitude oscillations, demonstrated in Fig. 5. Only a very small triangular region of the near field remains truly a plane wave: in the proximity of the source the plane wave and the edge wave do not yet interfere (Kramer et al., 1988). It is also worth mentioning that the second harmonic beam is somewhat narrower than the fundamental beam. This can be fully appreciated at greater distances in Duck (2002), where the pressure distributions are presented up to the far field.

The deviation from plane wave theory can be accounted for by the diffraction correction term. For example, Dunn et al. (1982) considered both attenuation and diffraction effects, leading to the following expression for the 2nd harmonic:

\[ P_2(z) = \left( \frac{2 + B/A}{2 \rho_0 c_0} \right) P_1^2(0) e^{-(s_1 + s_2/2)z} F(z), \tag{30} \]

where \( F(z) \) is the diffraction correction factor, described in detail in Ingenito and Williams (1971) and Williams (1951). Alternatively, the diffraction corrections developed using Multi-Gaussian beams have also been utilized (Haumesser and Meulen, 2019; Jeong et al., 2017; Jeong et al., 2015; Jeong et al., 2016).

The theory above serves the basis of the FAMs. Numerous works have estimated \( B/A \) through 2nd harmonic measurement [Eqs. (26)–(30)]. In most of these methods, the 2nd harmonic is measured in the near field of a plane piston source, enabling the plane wave approximation. Therefore, these conditions are implied throughout this section (Sec. VB) unless otherwise stated. These

![FIG. 3. (Color online) Schematic illustration of the setup used in optical methods/light diffraction methods for \( B/A \) measurement (top view). Detailed representations of such setups can be found in Adler and Hiedemann (1962) and Mikhailov and Shutilov (1959).](https://doi.org/10.1121/10.0003627)

![FIG. 4. (Color online) Illustration of the waveform deformation. The image shows the positive half-cycles of an undistorted sinus wave (solid line), and of a distorted wave (dashed line), where the distance \( w_1 \) is the distance between the maxima of these waves, and \( w_0 \) is the distance between points C and D, which are the intersections of the tangents at points A and B.](https://doi.org/10.1121/10.0003627)
methods are presented in two sections: measurements of homogeneous media (Sec. VB2) and heterogeneous media (Sec. VB3).

2. B/A measurement of homogeneous media

The studies discussed in this section assume invariant B/A along the beam path in the medium, yielding a single B/A value. All the strategies suitable for bulk estimation of B/A through 2nd harmonic measurement are presented below. All the presented works, unless otherwise mentioned, utilized the setup as in Fig. 2. Unlike the wave shape method, in this case, the receiver has to be responsive at the 2nd harmonic of the fundamental signal, transmitted by the source.

a. Second harmonic maximum. Equation (29) formed the basis for one of the early B/A measurement approaches (Beyer, 1960; Keck and Beyer, 1960). One can find the distance to the source where the 2nd harmonic reaches its maximum value by differentiating Eq. (29) with respect to z and finding the zero crossing. Once the coordinate of the 2nd harmonic maximum is determined experimentally, B/A can thus be calculated.

b. Extrapolation scheme. Other strategies utilized the lossless formulation in Eq. (26). It has been experimentally verified (Krasilnikov et al., 1957) that at distances close to the source, the dependence of the 2nd harmonic on the distance z and the pressure at the source $P(0)$ follows the lossless model described by Eq. (26) also in a dissipative medium. Therefore, one can derive B/A by extrapolating the 2nd harmonic amplitude at zero distance from the source,

\[
\frac{B}{A} = \frac{2\rho_0 c_0}{\pi f} \left[ \frac{P_2(z)}{z P_1(0)^2} \right]_{z=0} - 2.
\]

(31)

For this purpose, Adler and Hiedemann (1962) utilized the optical setup (Fig. 3) to measure the transmitted fundamental signal $P_1(0)$ and the 2nd harmonic at different distances from the source transducer. Extrapolating $|P_2(z)|/z P_1(0)^2$ to $z=0$, as in Fig. 6, yielded $B/A$ for water and m-Xylene.

Law et al. (1981) and Dunn et al. (1982) utilized a much simpler setup (Fig. 2), measuring the 2nd harmonic amplitude $P_2$ and $P_1(0)$ with an additional planar transducer, also employed in all the following studies unless otherwise mentioned. For this purpose, a calibration procedure of the receiver is required, allowing us to convert measured voltage to pressure values and to determine $P_1(0)$. Extrapolating $|P_2(z)|/z P_1(0)^2$ to zero distance from the source, they obtained $B/A$ for several biological solutions as well as whole liver. When comparing their values to glycerol and glycerin, previously obtained by the thermodynamic method (Coppens et al., 1965), they concluded that this technique has an uncertainty of 10%.

Dunn et al. (1982) introduced attenuation in the expression for the 2nd harmonic [Eq. (28)], showing that $|P_2(z)|/z P_1(0)^2$ decreases exponentially with distance in the proximity of the transducer. Moreover, they were the first ones to consider diffraction effects [Eq. (30)] that manifested themselves in the calibration procedure (Williams, 1951) of the receiver as well as in the quantification of the 2nd harmonic (Ingenito and Williams, 1971). Law et al. (1985) followed the same procedure as Dunn...
et al. (1982) to measure $B/A$ of tissues, requiring the tissue sample to be sliced in order to obtain measurements at several distances.

The extrapolation scheme has an important advantage: it avoids measurements of the attenuation coefficient of the medium. As illustrated in Fig. 6, even if the attenuation value of the medium under study changes, the curves intersect at the same point, provided that the other acoustic parameters are equivalent. This method is sometimes referred to as the pullback method (Wallace et al., 2007).

c. Single measurement. Equations (27)–(30) also enable measuring $B/A$ from a single measurement once the attenuation coefficients at the fundamental $z_1$ and harmonic $z_2$ frequencies are known. After first estimating the attenuation coefficients, Cobb (1983) estimated $B/A$, taking diffraction of the 2nd harmonic (Ingenito and Williams, 1971) into account [for the case of transducers of equal size, Eq. (27)]. The authors noted that the approximation given by Eq. (28), justifying the extrapolation scheme, may lead to errors of 7% in samples such as water and glycerin (Dunn et al., 1982). Zhang and Dunn (1987) utilized Eq. (30) to estimate $B/A$ from a single acquisition, finding that there is no significant difference between $B/A$ of in vivo and ex vivo cat livers. In Haumesser and Meulen (2019), the second harmonic was measured after its reflection from an aluminum plate that replaced the receiver in a typical through-transmission setup (Fig. 2). The reflection mode method increased the propagation path of the signal in the studied medium. This way an accurate $B/A$ measurement could be acquired for a reduced amount of the investigated liquid. Li et al. (2017) presented a through-transmission method for $B/A$ measurement of fluids, utilizing focused transducers to transmit and receive acoustic signals. Diffraction corrections were derived for focused receiver and source and a simple calibration procedure of the receiver was proposed. This enabled estimating $B/A$ of water within an 8% error for multiple distances.

d. Source pressure-harmonic characteristic. Panfilova et al. (2018) and Pantea et al. (2013) determined $B/A$ of water based on Eqs. (27) and (28) by fitting a line to the dependence of the 2nd harmonic amplitude on the fundamental pressure $P_1(z)$. They require no attenuation measurement since they account for attenuation by using the fundamental and 2nd harmonic amplitudes at the measurement point. Pantea et al. (2013) reported more extensive work, performing the fit for a larger range of distances and making use of the extrapolation scheme or pullback method (Sec. V B 2 b).

Meulen and Haumesser (2008) implemented this method in echo-mode by the employment of a reflector, concluding that the reflector must have an impedance higher than that of the studied fluid. This ensures that the 2nd harmonic components generated during forth and backpropagation interfere constructively, and $B/A$ quantification is possible. Otherwise, these components add out of phase.

Similarly, Chitnalah et al. (2007) recorded the 2nd harmonic in reflection mode at different source pressures but reflected from the interface of two liquids. They took into account attenuation and diffraction correction, decomposing the source function into a series of Gaussian beams.

e. Comparative method. Transmission mode comparative method. The first record of the comparative method was found in Gong et al. (1963). Its aim is to avoid absolute pressure measurements and therefore a receiver calibration procedure. The idea of the method is to compare the 2nd harmonic signal relative to that generated in a medium with a known $B/A$ when the measurements are performed at the same source pressure and distance $L$ from the source (Fig. 2). This way, when describing the 2nd harmonic component with Eq. (26) for both media, and taking their ratio, one can derive that

$$\frac{B}{A}_m = \frac{P_{2m}(\rho_0 C_0^3)}{P_{20}C_{00}} \left(\frac{B}{A}_0 + 2\right) - 2, \quad (32)$$

where the subscripts $m$ and 0 denote the medium under study and the reference medium, respectively. In this first study, the reference liquid was acetone, with a density and speed of sound close to that of the studied nitrogen. However, most studies use water as the reference medium, as its $B/A$ is well known and attenuation can be neglected. Gong et al. (1984) and Zhang et al. (1991) utilized the same technique, with the latter work also accounting for diffraction effects.

Wallace et al. (2007) used a hybrid of the extrapolation and comparative methods. The authors compared the ratio $V_2(z)/V_1(0)^2$ of isopropanol to that of water, where $V_1$ and $V_2$ are the voltages associated with the fundamental and the 2nd harmonic. Differently from previous works, the authors took into account the fact that the generated source pressure actually depends on the medium where the source is immersed (also explained in Jackson et al., 2014), defined by the transmission coefficient between the transducer material and the medium [see also Eq. (34)]. Besides this, they introduced a steel delay line in front of the transmitting transducer. Since steel has a speed of sound that is approximately four times higher than in water, the resulting diffraction pattern is compressed compared to that in water. This allowed positioning the natural focus inside or right after the path in steel. As a result, Wallace et al. (2007) satisfy the plane wave approximation by measuring in the far field, requiring no further diffraction corrections.

Yu et al. (2014) performed an evaluation of the comparative technique, including simulations and a phantom experiment for homogeneous tissue. The simulation study utilized a linear probe as the source and measured $\beta$ for 3 tissue types at different distances. The experiment showed that the estimated $\beta$ did not depend significantly on the measurement distance, demonstrating the method’s robustness. The authors took into account tissue attenuation [Eq. (28)]. In this work, the formula for $B/A$ was derived from the special
case of the comparative method: the finite amplitude insert substitution (FAIS) technique explained below in Sec. IV B 2 f). This resulted in an erroneous formula. However, since the transmission coefficients of the studied tissues were close to unity, the introduced error was very small. The authors assessed their technique to be within 3% of uncertainty.

Reflection mode comparative method. Kourtiche et al. (2001) used the same transducer to transmit the fundamental and receive the 2nd harmonic reflected from a reflector plate. In this case, the 2nd harmonic generation occurs both ways. The authors also performed an analysis of the electromechanical behavior of the transducer at different transmit frequencies. A transducer generates a “clean” and strong fundamental around its resonance frequency. At the same time, it must be sensitive enough to detect the 2nd harmonic of the transmitted signal. Therefore, a favorable trade-off frequency region must be determined for B/A estimation. Besides this, a transducer usually shows different sensitivities in transmission and in receiving. These are influenced by the impedance of the transducer, which varies with signal frequency and the impedance of the medium. The authors showed that neglecting these effects can lead to errors in B/A estimation and that there is a frequency range where B/A can be estimated most accurately. This work is relevant for all echo-mode developments as well as transmission mode measurements utilizing identical transducers as source and receiver.

f. FAIS method. Transmission mode FAIS. The FAIS method was motivated by the idea of avoiding absolute pressure measurements, similar to the comparative method. Some authors classify the comparative method (Sec. IV B 2 e) as a particular case of FAIS (Yu et al., 2014), which in reality was developed later. In light of this, it should be noted that the equation utilized for the comparative method should not be derived as a general case of the FAIS. With FAIS, the medium under study is inserted in a water path and does not have the same length as the reference medium (water), in most cases resulting in 2 reflection interfaces (Fig. 7). Initially, Shklovskaya-Kordi (1963) developed this method based on the Fubini solution [Eq. (26)] for measurement of internal pressure through B/A. When the source pressure and distance between the source and receiver (L) are fixed (in this work kept within the near field distance to adhere to the plane wave approximation), the amplitude of the 2nd harmonic in a water path after the sample negligible. Because of this, the sample is conventionally positioned close to the receiver in all FAIS modifications. As for the comparative method, FAIS does not require transducer calibration for recovery of the absolute pressure values since the pressure ratio term is equivalent to the received voltage ratio. Gong et al. (1989) built on this method, introducing an attenuation correction in Eq. (28) aimed at measuring B/A of tissue, making the assumption that \((x_2 - 2x_1)\) is small, valid for most tissues as they have a nearly linear frequency dependence (Duck, 1990; Goss et al., 1979). The resulting expression is

\[
\left(\frac{B}{A}\right)_{m} = \frac{P_{2m}L}{P_{20}d} \left(\frac{D'}{D''}\right) - \frac{(L/d)^{-1}}{1} \left(\frac{D'}{D''}\right) \left[\left(\frac{B}{A}\right)_0 + 2\right] - 2.
\]

Equation (33) is only valid when the investigated medium is nearly lossless. Moreover, the formula was derived merging the 2nd harmonic contribution from water before the sample and after it, which is justified if the acoustic impedance of the medium is close to water. Alternatively, the medium can be placed very close to the receiver, making the 2nd harmonic generation in the water path after the sample negligible. Because of this, the sample is conventionally positioned close to the receiver in all FAIS modifications. As for the comparative method, FAIS does not require transducer calibration for recovery of the absolute pressure values since the pressure ratio term is equivalent to the received voltage ratio. Gong et al. (1989) built on this method, introducing an attenuation correction in Eq. (28) aimed at measuring B/A of tissue, making the assumption that \((x_2 - 2x_1)\) is small, valid for most tissues as they have a nearly linear frequency dependence (Duck, 1990; Goss et al., 1979). The resulting expression is

\[
\left(\frac{B}{A}\right)_{m} = \frac{P_{2m}L}{P_{20}d} \left(\frac{D'}{D''}\right) - \frac{(L/d)^{-1}}{1} \left(\frac{D'}{D''}\right) \left[\left(\frac{B}{A}\right)_0 + 2\right] - 2.
\]

Here, one can see that a measurement of the attenuation coefficient at the fundamental \(x_1\) and the harmonic \(x_2\) is required for B/A determination. Besides this, Gong et al. (1989) also introduced a diffraction correction which for most biological tissues (speeds of sound: 1400–1600 m/s) they quantified to be within 2%. However, it must be noted that, in general, for liquids with a speed of sound further away from that of water, the diffraction correction can introduce significant errors (e.g., 5% error for ethanol).

Wu and Tong (1998) measured B/A of contrast agents. Since B/A of contrast agents can be on the order of hundreds and thousands, the harmonic component generated in water can be neglected for the configuration in Fig. 7. This resulted in a simpler expression. No diffraction correction was used, possibly due to the assumption of a similar speed of sound in contrast agents to that of water (not stated).

Dong et al. (1999) derived a formula analogous to Eq. (35), however, they utilized the general expression for
attenuation in Eq. (27). Dong et al. (1999) positioned the sample and the receiver in the extreme far field of the source, another region of the piston field where the plane wave approximation may be considered valid. The authors removed all harmonic content generated in the near field by placing an acoustic absorber before the sample. Yet, due to the absorber, the insonifying amplitude is expected to have been low, and the resulting distortion weak. Cortela et al. (2020) and King et al. (2011) utilized the same configuration as Dong et al. (1999) to measure B/A of gellan gum-based tissue-mimicking phantoms. Choi et al. (2011) utilized the same formula as Dong et al. (1999) in a setup where no acoustic absorber was used. They presented the temperature dependence of B/A of porcine liver.

Harris et al. (2007) proposed another setup that allowed avoiding diffraction correction. Their solution was a large source transducer (8 cm in diameter), which provided a broad plane wave region, without diffraction effects. Figure 5 demonstrates such a triangular region in the proximity of the transducer, where the field is stable.

Kujawiska et al. (2003) introduced a modified FAIS method. A model of the ratio $P_{2n}/P_{20}$ depending on sample thickness $d$ was fit to experimental data when using a small receiver (0.4 mm in diameter). The best fit of the data provided an estimate $B/A$ for liquids and homogenized tissue. The current approach required no plane wave assumption.

Zeqiri et al. (2015) conducted a detailed analysis of the influence of several factors on the accuracy of $B/A$ measurement with the FAIS, e.g., sample positioning with respect to the receiver, source pressure amplitude, and sample thickness.

Reflection mode FAIS. Lu et al. (2004) utilized FAIS in reflection mode, transmitting and receiving with the same compound transducer whose inner ring served as the source, and outer ring received the signal from a reflector plate. However, the observed $B/A$ was variable on a microscale.

Nonlinear acoustic microscopy. Acoustic microscopy allows studies of small-volume samples (e.g., 0.1 mL; Saito, 2010). It utilizes high frequency sources (14–19 MHz) in conjunction with acoustic lenses that provide a short focal distance (e.g., 2.3 mm; Germain et al., 1989). Altogether, this produces appreciable nonlinear effects in the focal spot already at such short distances. All the studies in this field have adapted the comparative and FAIS techniques using water as a reference medium and either completely filling the space by the sample, or positioning it only in the focal region, surrounded by water.

Banchet et al. (2000), Banchet and Cheeke (2000), and Germain et al. (1989) developed an acoustic microscope for the measurement of B/A. The 2nd harmonic was detected by a planar transducer. Its generation was assumed to be confined to the focal region and was described with plane wave theory utilizing Eq. (28). This system also allowed measuring sound velocities; however, parameters like density and attenuation needed to be measured beforehand to enable calculations with Eq. (28).

Additional work in this direction was performed in Saito (1999a,b, 2010), Saito and Kim (2011), and Saito et al. (2005). The final setup of the developed system utilized the source as a receiver, detecting the signal from a reflector. The authors made use of Gaussian beam theory that models the field as a series of beams whose spatial pressure distribution is described by the Gaussian function (Kim et al., 2006). This system allowed measurement of B/A as well as linear acoustic parameters, including sample density. At the latest stage of development, Saito and Kim (2011) generated two-dimensional (2D) images of B/A and linear acoustic parameters by mechanically translating the samples of biological tissues (e.g., fat vs nonfat; coagulated vs normal), showing that tissue B/A was variable on a microscale and exhibited different variation patterns than the linear parameters (e.g., attenuation, density). In Saito (2010) and Saito and Kim (2011) the authors observed good reproducibility of their measurements (within 1%) and stated the measurement error to be within 10%, typical for FAMs.

g. Transmission line method. Dong et al. (2006) and Kushibiki et al. (1997) introduced a novel method utilizing frequencies as high as 100–200 MHz. The specimen was positioned between two SiO$_2$ buffer rods with transducers at their outer ends. SiO$_2$ has a negative $\beta$: its 2nd harmonic shows an opposite phase compared to that generated in liquid. This way, when acquiring $P_2$ for different sample lengths, at a certain point the 2nd harmonic was cancelled out completely. The authors utilized plane wave theory [Eq. (27)], incorporating diffraction and dispersion in Kushibiki et al. (1997), showing that this gives more stable B/A estimates. The major advantage of this method is that no pressure measurement is needed. However, the observed $\beta$ for water was 20% higher than the value reported in literature. This was ascribed by the authors to uncertainties in the properties of SiO$_2$.

3. B/A imaging

The studies discussed in this section consider B/A estimation in heterogeneous media. First, the section performing through-transmission measurements is presented. In this case, the image is reconstructed with computer tomography (CT) once the through-transmission measurement is repeated for several sample rotation and translation configurations (Fig. 8). The reconstruction is obtained by use of the Radon transform with the resulting image resolution being determined by the number of employed rotation angles. The reflection-mode measurement follows the same scheme, however, using the source as the receiver. After transmission through the tissue, the signal is reflected from a reflective plate on the opposite side of the sample. Echo-mode imaging is the last family of methods presented in this section. In this case, the signal is received by the source transducer as it is reflected along its
The reference medium was water, making it possible to utilize a scattered signal different values of \(\beta, z_1, z_2\) correspond to every \(z\),

\[
P_{2m}(L) = \frac{\pi f_2 P_1(0)^2}{2(\rho_0 c_0^2 m)} \int_0^L \beta_m(z) \exp \left( \int_0^z -2z_1(z)dz \right.
\]

\[
- \int_z^L z_2(z)dz \right) dz,
\]

(36)

where the indice \(m\) refers to the medium under investigation. In order to avoid conversion to absolute pressure values, the authors also measure the amplitude of the 2nd harmonic \(P_2(L)\) in a homogeneous reference medium with a known \(\beta\). The reference medium was water, making it possible to apply the lossless Fubini solution [Eq. (26)],

\[
P_{20}(L) = \frac{\pi f_2 P_1(0)^2}{2(\rho_0 c_0^2)} L \beta_0.
\]

(37)

This way, when the sample is placed in the water path between the source and the receiver, the ratio of the received 2nd harmonics is defined by

\[
P = \frac{P_{2m}(L)}{P_{20}(L)} = \frac{(\rho_0 c_0^2 m) \beta_0}{(\rho_0 c_0^2)} \int_0^L \beta_m(z) \exp \left( \int_0^z -2z_1(z)dz \right.
\]

\[
- \int_z^L z_2(z)dz \right) dz.
\]

(38)

The implemented CT system allowed for rotation of the sample and translation of the source and receiver (hydrophone) along the sample length (Fig. 8). The receiver was positioned in the near field of the transmitting transducer. The obtained projection images of the ratio \(P\) [Eq. (38)] were transferred to the \(\beta\) domain by the filtered convolution method and then corrected by multiplying with the attenuation matrix describing the sample’s attenuation in space (estimated by attenuation tomography with the same setup). This work showed promising results; however, the authors concluded that attenuation and velocity estimates required further improvement. Yu et al. (2014) also simulated B/A tomography based on Eq. (38), modified for the case of an attenuating reference medium and utilizing a filtered back projection algorithm.

b. \(\beta\) tomography in reflection mode. Gong et al. (2004) extended their previous work (Zhang et al., 1996) to reflection tomography. The tissue sample was positioned in water between the source and a reflective plate, where the reflective plate replaced the receiver in Fig. 8. Equation (38) was extended, now containing nonlinear generation and attenuation terms for the forward and backward path. Figure 9 presents an example of an image acquired in this work. In this image, we can see a two-layered tissue structure with porcine liver surrounded by porcine fat, submerged in water.

c. \(\beta\) imaging in echo-mode. Reflection mode imaging poses additional challenges, compared to transmission tomography. In the latter case, the recorded signal has travelled through the whole bulk of the tissue, and therefore, the effect of varying scatterer density within the medium is averaged out. However, when utilizing echo-mode \(\beta\) imaging, the strength of the reflected echoes is, to a large extent, defined by the scatterer density at each reflection point (Waag, 1984), masking information about other acoustic properties. To cancel out the scatterer effect, scientists normalized the recorded signal to a signal that is assumed to have an analogous scattering pattern. Three different reference signals have been identified in literature. One utilizes an additional signal, transmitted at the 2nd harmonic frequency. Another utilizes the second harmonic amplitude reflected from a scattering homogeneous reference medium. The last reference signal is the reflected fundamental component of the received pulse.

Akiyama (2000) and Fujii et al. (2004) found a way to mitigate the influence of scatterers by assuming that the scatterer distribution affects a signal of a certain frequency in the same way, whether it is the generated 2nd harmonic at \(2f_0\) of the fundamental at \(f_0\), or whether it is the transmitted fundamental at \(2f_0\). The authors assumed that the 2nd harmonic is generated only in transmission, and not on the way back when reflected from scatterers due to low amplitudes of the reflected signal. Attenuation was taken into account in both directions of propagation, leading to

\[
P_{20}(z) = \frac{1}{2} \left( f_0 \right)^2 \left( \frac{B/A + 2}{4\rho_0 c_0^3} \right) \int_0^z x(f_0, z)dz
\]

\[
- \int_0^z \gamma(f_2, z) \left( f_2, z \right) \frac{(B/A + 2)2\pi f_0}{4\rho_0 c_0^3} dz.
\]

(39)
where \( \rho \) and \( c \) are medium properties, assumed constant and \( \gamma(2f_0, z) \) is the backscattering characteristic term. The received fundamental when transmitting a 2nd pulse at \( 2f_0 \) is also proportional to \( \gamma(2f_0, z) \), and \( \int x(2f_0, z)dz \). Therefore, the ratio of the generated 2nd harmonic to the fundamental at the frequency of the 2nd harmonic cancels out the backscattering and the attenuation at \( 2f_0 \) terms. The authors extracted \( h(z) \), a parameter defined by \( B/A \), speed of sound and density of the medium with the following equation:

\[
h(z) = \frac{A_0(0, 2f_0) d}{P_0^2(0, f_0) dz} \left[ \frac{P_{2h}(z)}{P_{2f}(z)} \right],
\]

(40)

where \( P_0 \) and \( A_0 \) are pressures at the source when transmitting at \( f_0 \) and \( 2f_0 \), respectively. Signals \( P_{2h}(z) \) and \( P_{2f}(z) \) are the received 2 harmonic and fundamental at \( 2f_0 \), correspondingly. It is important to note that the studies mentioned above retrieved one single value of \( h \), fitting a line to the ratio \( P_{2h}(z)/P_{2f}(z) \) observed throughout the whole sample depth. Besides a phantom study, Fujii et al. (2004) conducted an in vivo clinical study with 41 patients, using \( h \) as a single-valued indicator of liver fat content.

A similar strategy was followed by Gong et al. (2004) and Liu et al. (2008) who acquired C-scan images of the \( B/A \) profile, modifying Eq. (40),

\[
\frac{B}{A}(z) = \frac{4P_0c_0^3 A_0(0, 2f_0) d}{c_0^2(0, f_0) dz} \left[ \frac{P_{2h}(2f_0, z)}{P_{2f}(2f_0, z)} \right] - 2,
\]

(41)

assessing the local slope of the ratio \( P_{2h}(2f_0, z)/P_{2f}(2f_0, z) \) of the echoes reflected by tissue. The authors showed very promising discrimination capabilities, when imaging heterogeneous tissue models in the plane perpendicular to the beam propagation direction, by mechanically scanning their system point by point. No capabilities of \( B/A \) discrimination in depth of the sample were presented.

Varray et al. (2011b) extended the comparative method [Eqs. (36) and (27)] to enable imaging of heterogeneous media in echo mode. By taking several acquisition lines in the filtered 2nd harmonic image as a reference, the authors normalized the 2nd harmonic response of the whole image to construct a \( \beta \) image. The images of two phantoms with inclusions were acquired with the ULA-OP scanner (X-Phase), transmitting a focused beam. Experimental images acquired with this strategy in other works (Toulemonde et al., 2014; van Sloun et al., 2015) are presented in Figs. 10 and 11. van Sloun et al. (2015) eliminated the influence of scatterer density, expressing \( \beta(z) = f(P_{2h}(z)/P_f(z)) \) as a function of the ratio of the received amplitudes of the 2nd harmonic to the fundamental, derived from the 1D lossy Westervelt equation [Eq. (8)]. The proposed approach was called "the harmonic ratio method." Simulations were performed with the iterative nonlinear contrast source approach, capable of modelling 3D fields in complex media (Demi et al., 2011). The modelled media exhibited different \( \beta \) and \( x \) values with the same constant speed of sound and density. The resulting images showed good contrast. A more realistic tissue-mimicking phantom acquisition was performed with the ULA-OP scanner, acquiring 128 radio frequency (RF) lines. van Sloun et al. (2015) compared the proposed method to the extended comparative method (Varray et al., 2011b) and direct estimation of \( \beta \) from the 2nd harmonic amplitude [Secs. VB2c and VB1, Eqs. (27)–(30)]. The two phantom layers had different oil content and were, therefore, expected to have different \( \beta \). The resulting normalized \( \beta \) images of the phantom for the three studied strategies are presented in Fig. 10. All methods showed capable of distinguishing two layers with different oil content. However, the strategy proposed in van Sloun et al. (2015) showed more homogeneous estimates for both layers and better consistency over depth. Unfortunately, no follow-up experimental work further confirmed the applicability of this method in a realistic clinical setting.

Another in silico work Toulemonde et al. (2014) proposed utilizing the extended comparative method (Varray et al., 2011b) on compounded B-mode images acquired with high frame rate plane wave imaging. Utilizing plane waves allowed imaging at various depths compared to focused beams (Varray et al., 2011b) while compounding reduced the speckle. Moreover, to reduce the speckle, filtered second harmonic images were normalized by the corresponding filtered fundamental images. These normalized second harmonic signals were compared to those of the reference medium to extract the \( B/A \) distribution. This way, Toulemonde et al. (2014) proposed utilizing two types of signals to reduce the influence of scatterers on \( B/A \) estimation: the fundamental of the received signal and the received 2nd harmonic of a reference medium. This approach resulted in a more accurate \( B/A \) reconstruction of a simple \( B/A \) distribution than with the original extended comparative method in Varray et al. (2011b). Nevertheless, \( B/A \) images of a simulated medium with a complex \( B/A \) distribution were greatly degraded by the remaining speckle pattern for both methods. Further, this approach was extended to multi-taper coherent plane wave compounding (Toulemonde et al., 2015) using several orthogonal apodizations for plane wave beamforming, creating several speckle patterns for each steering angle. Toulemonde et al. (2015) presented \( B/A \) images of in silico and experimental phantoms, showing a better \( B/A \) delineation compared to previous approaches.
Experimental images of a three-layered tissue-mimicking phantom are presented in Fig. 11.

C. Fundamental nonlinear absorption

1. Basic theory

When observing an increase in absorption with signal intensity (Fox and Rock, 1941), this was first attributed to cavitation. Later, however, it was recognized (Fox and Wallace, 1954) to be the result of energy transfer from the fundamental to higher harmonics. Moreover, as nonlinear effects grow with the source amplitude [e.g., Eq. (26)], nonlinear attenuation increases along with them, limiting the power that can be possibly delivered to a certain depth (Fig. 12) (Hikata et al., 1980; Kashkooli et al., 1987).

In the shock-free or pre-shock region ($\sigma < 1$) of a lossless medium, the fundamental component of a plane wave will decrease according to Eq. (42) due to energy transfer to higher harmonics (Fubini-Ghiron, 1935),

$$P_1(z) = P_0 \left(1 - \frac{1}{8} \sigma^2 \right)$$

$$= P_0 \left(1 - \frac{1}{2} \left[ \frac{1 + \frac{1}{2} A B}{\rho C f_0^3} P_0 \right]^2 \right).$$

Additional small-signal attenuation losses can be accounted for by the Keck and Beyer solution (Keck and Beyer, 1960) for the fundamental.

Another way to account for both effects of small-signal attenuation and nonlinear depletion of plane waves was proposed by Bartram (1972) and Rudnick (1952), introducing spatial changes that are ascribed to the rate of heat production due to fluid heating by the shock fronts and energy loss between shocks.
\[
\frac{dp(z)}{dz} = -\alpha p - \frac{\beta f z}{\rho_0 c_0} p^2.
\] (43)

The equation above was first introduced for weak shock theory ($\sigma > 3$); however, it has also been adapted by Kashkooli et al. (1987) to describe the fundamental amplitude change at $\sigma < 3$, the proposed solution being

\[
P(z) = P(0)e^{-\alpha z}\left[1 + \frac{(1 - e^{-\alpha z})^2}{\alpha \rho_0 c_0 z}\right].
\] (44)

When the source pressure is low, the dominating term in Eq. (44) is the first one on the right hand side, describing small-signal attenuation, and corresponding to the linear region in Fig. 12. However, as the source pressure increases, the harmonics grow, depleting the fundamental harmonic as described by the 2nd term in Eq. (44) and corresponding to the saturating process in Fig. 12.

2. B/A measurement of homogeneous media

a. Transmission mode. Hikata et al. (1980) and Kashkooli et al. (1987) used the finite amplitude loss technique (FALT) based on Eq. (44). The authors performed a transmission measurement, where the dependence of the received signal pressure $P(z)$ on the intensity of the transmitted signal pressure $P(0)$ was recorded at a fixed distance. When expressing the dependence of $P(0)/P(z)$ via $P(0)$, they extracted $\beta$ from the slope of this linear dependence. The authors discuss the trend of the FALT to yield values, higher than those acquired with the thermodynamic method (Sec. III) and from light diffraction (Sec. VA1). Even though limited to homogeneous media, the method is rather simple, requiring a pair of transducers with a similar resonance frequency. The internal consistency of the measurements was stated to be 10% (Kashkooli et al., 1987).

b. Echo-mode. Byra et al. (2017) applied the lossless plane wave theory [Eq. (42)] to determine B/A of water.

Typical for echo-mode imaging, it was assumed that the backscattered waves travelled linearly. The Verasonics research scanner (Verasonics, Inc.) equipped with a linear array probe L12–5 was used to image a set of reflecting wires positioned at different depths in water. By sending progressively increasing pressure values, the authors were able to observe a portion of the fundamental saturation (Fig. 12) and by fitting Eq. (42) to this curve extract water’s $\beta$.

3. B/A imaging

All B/A imaging works, based on the registration of the fundamental amplitude, were performed in echo-mode. Linuma (1988) patented the approach of detecting fundamental saturation already in 1988 when utilizing an array transducer. A simple approximate equation was used to describe the received pressure $P_{rec}$, depending on the transmitted pressure $P_{trans}$,

\[
P_{rec} = \frac{P_{trans}}{1+aP_{trans}},
\] (45)

where $a$ is the parameter reflecting nonlinear effects, equal to 0 if nonlinear effects are absent.

Nikoonahad and Liu (1990) utilized a similar approach. However, actual B/A values were determined and a single-frequency pulse was used. The authors utilized the approximate analytical solution to a nonlinear differential equation in terms of density fluctuations (Tjotta and Tjotta, 1981), determining B/A from the fundamental depletion of echoes as the source pressure was progressively increased. Diffraction effects were cancelled out by taking the ratio of two signals received at different source pressures. The theory was validated with simulations and an experimental measurement in ethylene glycol after a calibration procedure in water. The authors also showed in Nikoonahad and Liu (1989) that it was possible to resolve B/A of a phantom with heterogeneous liquid layers by taking track of the pulse’s history and using a recursive algorithm. Nikoonahad and Liu (1989) stated that the applicability of the method to tissue still had to be investigated, since the high viscous losses in tissue may not allow for sufficient fundamental depletion at safe pressure levels.

Aiming to enable real-time B/A assessment, Fatemi and Greenleaf (1996) adapted the theory from Nikoonahad and Liu (1990), limiting the number of transmissions to two: one at a low amplitude in the linear regime, and another at a high amplitude with prominent nonlinear phenomena. The authors generated images in which shadows reflected non-linearity of preceding regions, in a manner in which attenuation manifests itself on B-mode images, as well as relative B/A images. The authors imaged the nonlinearity of ethanol and water, as well as fat-muscle structures, and tissue-water and tissue-contrast agent structures, concluding that the method can effectively identify regions of elevated nonlinearity.

In conclusion, several works utilizing the depletion of the fundamental to measure B/A have been presented.
Utilizing the fundamental is practical, since in most pulse-echo systems the receiving transducer has a relative bandwidth of 50%–70%, making it challenging to detect harmonics with a good signal-to-noise ratio (SNR) (Fatemi and Greenleaf, 1996).

VI. PARAMETRIC ARRAY

The concept of the parametric array was introduced to acoustics by Westervelt (1963), stating that two collimated coaxial acoustic beams, approximated by plane waves, generate the sum and difference frequency waves (secondary waves). The secondary waves represent narrow beams, whose amplitude is proportional to the parameter of nonlinearity $\beta$ of the propagation medium and rises linearly with distance from the probe $z_0$.

$$P_s(z_0) = \frac{S_0 \omega_0^2}{4 \pi \rho_0 c_0^3} \beta P_1(0) P_2(0) \times \int_0^{z_0} \exp(-\alpha_1 + \alpha_2) z - \alpha_3(z_0 - z) \frac{dz}{z_0 - z}. \quad (46)$$

Equation (46) is intended for homogeneous media, where $P_s$ and $\alpha_i$ are the pressure amplitude and attenuation coefficient of the secondary wave, $P_1(0)$ and $P_2(0)$ are amplitudes of primary beams at the source, $\alpha_1$ and $\alpha_2$ are their attenuation coefficients, and $S_0$ is the beam cross-sectional area of the primary beams. The difference frequency wave undergoes lower attenuation compared to the sum component. Therefore, if two source frequencies are close to each other, the difference frequency wave is simpler to detect compared to the sum component. In the contrary situation, the sum component may be more favorable since $P_s$ is proportional to $\omega_0$. Detection of the difference or sum frequency component provides a means of $\beta$ measurement, called the parametric array method.

The possibility of $\beta$ measurement with the parametric array was first demonstrated in Nakagawa et al. (1984), when the finite amplitude and thermodynamic methods were already actively used and compared (Law et al., 1983, 1985). In a configuration when a dual-frequency voltage pulse was transmitted by a transducer and detected by a hydrophone in a transmit-mode configuration, the authors estimated $\beta$ of an agar gel phantom by comparing the amplitude of the difference frequency wave in water to that of an agar gel phantom. Here, attenuation effects were taken into account, and $\beta$ was estimated as an average uniform value. In the same paper, Nakagawa et al. (1984) extended this method to CT using a conventional system (Fig. 8), generating the first CT images acquired with the parametric array method. This work was further continued in Nakagawa et al. (1986), confirming that attenuation and $\beta$ images could be acquired with the proposed system and discovering that the estimation of attenuation was heavily influenced by refraction, causing errors in $\beta$ reconstruction. Nakagawa et al. (1986) and Nakagawa et al. (1984) used the Westervelt equation to model the secondary wave propagation [Eq. (46)]. Since an accurate estimation of $S_0$ poses a problem, the $\beta$ value can only be estimated when comparing the secondary wave sound pressure generated in the sample to that of a medium with a known $\beta$. Arnold et al. (1987) and Nakagawa et al. (1986) simplified the analysis of the parametric array method by describing it with the Burgers equation [Eq. (10)] rather than the Lighthill’s exact equation for arbitrary fluid motion used by Westervelt (Westervelt, 1963). The solution of the Burgers equation for homogeneous media is

$$P_s(z_0) = -\frac{\omega_0 P_1(0) P_2(0)}{\rho_0 c_0^3} \beta \times \int_0^{z_0} \exp[-(\alpha_1 + \alpha_2) z - \alpha_3(z_0 - z)] \frac{dz}{z_0 - z}. \quad (47)$$

This allowed for direct $\beta$ reconstruction from the registered primary wave amplitudes, and estimated attenuation

### Table VI. Summary of parametric array works.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of assessment, imaged parameter</th>
<th>Investigated media</th>
<th>Uncert., %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakagawa et al., 1984</td>
<td>Single measurement (for homogeneous Media), $\beta$, $\gamma$, $\beta_0$ tomography, $\beta_0$</td>
<td>Agar gel phantom</td>
<td>—</td>
</tr>
<tr>
<td>Arnold et al., 1987; Nakagawa et al., 1986</td>
<td>Tomography, $\beta$</td>
<td>Phantoms with inclusions</td>
<td>—</td>
</tr>
<tr>
<td>Cai et al., 1992</td>
<td>In silico diffraction tomography, $\beta$</td>
<td>Simulated weakly, moderately, and strongly scattering objects</td>
<td>—</td>
</tr>
<tr>
<td>Zhang et al., 2001a</td>
<td>In silico tomography, $\beta$</td>
<td>Simulated fluids, biological tissues</td>
<td>&lt;1 (in silico experiment)</td>
</tr>
<tr>
<td>Zhang et al., 2001b</td>
<td>Tomography, $\beta$</td>
<td>Tissue phantoms with water, porcine liver and fat, pathologic liver; boiled egg</td>
<td>10 (tissue)</td>
</tr>
<tr>
<td>Wang et al., 2003</td>
<td>Reflection tomography, $\beta$</td>
<td>Normal and pathological porcine liver</td>
<td>5 (tissue)</td>
</tr>
<tr>
<td>Barrière and Royer, 2000, 2001</td>
<td>Single measurement (for homogeneous liquid media), $\beta$</td>
<td>Ethanol, water</td>
<td>2–5 (liquid)</td>
</tr>
<tr>
<td>Bereza et al., 2008; Burov et al., 2006</td>
<td>Tomography (noncollinear parametric interaction), variation of $\beta$</td>
<td>Wool fibre, hog fat in water</td>
<td>—</td>
</tr>
</tbody>
</table>
compensation. Just as for previous studies, the source of errors in primary wave data and the attenuation correction term were attributed to diffraction or refraction effects. Diffraction tomography was proposed as a solution to this problem. The possibilities of diffraction tomography were studied based on theory and simulations in Cai et al. (1992), where the authors had to come back to the equation initially derived by Westervelt (1963) to include the diffraction effect for weakly, moderately, and strongly scattering objects. The presented simulations show the ability to reconstruct the β profile; however, these findings, to our knowledge, were not experimentally confirmed.

Another group (Zhang et al., 2001a) used Eq. (47) to express the secondary wave amplitude. However, they used the ratio of the secondary wave pressure amplitude after and before inserting the specimen as the projection data, adapting the insert substitution method introduced for the 2nd harmonic (Gong et al., 1989) to the parametric array method. They calculated the sound field produced by a piston source, representing the primary beams as a superposition of Gaussian beams. This way the authors, for the first time, demonstrated, based on theoretical analysis, that the amplitude of the difference frequency wave is nearly proportional to the distance from the source (reducing possible diffraction errors) and has no side lobes. For these reasons, they concluded that the parametric array method provides a better source to image β, granting higher resolution and higher accuracy compared to the 2nd harmonic. The authors showed the feasibility of the proposed CT method for β imaging with computer simulations. A follow-up with experimental results was published in Zhang et al. (2001b), confirming theoretical considerations regarding the secondary wave profile. CT images of phantoms with different β configurations, reasonably agreeing with previous β measurement results of other methods, were presented. The authors did not take diffraction effects into account, considering their influence reduced due to the stable rise of the difference frequency component, and the use of the FAIS method. In Wang et al. (2003), the group extended their work from Zhang et al. (2001a) to reflection mode imaging, presenting the theoretical analysis and the developed imaging system. They used a compound transducer as a transmitter and receiver, recording the signals reflected from an aluminium plate located behind the sample of interest. The images showed promise, detecting a difference between healthy, fatty, and hepatocirrhosis liver tissue. The same strategy was utilized in Gong et al. (2004), acquiring the image of a three-layered medium in Fig. 13: porcine liver surrounded by porcine fat, submerged in water.

Barrière and Royer (2000, 2001) introduced a new setup for β measurement of liquid media. They showed that the interaction of two primary beams with a high frequency ratio (>10) is equivalent to the phase modulation of the high-frequency wave. In a configuration where the two source transducers are on opposite sides of the sample chamber, a low frequency pulse with a velocity potential $\psi_2$ modulates a high frequency plane wave with a velocity potential $\psi_1$. An important contribution of this paper is the analysis of the diffraction effects based on plane wave expansions. The authors showed that in the case of two primary beams with a high frequency ratio (>10), the diffraction effect on the secondary wave is identical to that on the high frequency carrier wave. Therefore, since the presented method compares the amplitude of the secondary wave $\psi_1(r)$ to the high frequency primary wave $\psi(r)$ to extract β, the effect of diffraction is cancelled out. These observations were confirmed when the measured β values of water and ethanol showed good agreement with previously reported values. The authors also extend this methodology with a comparative method. In this case, no calibration of the low frequency transducer is needed, and the relative amplitude to that in water is used. The authors state the uncertainty of their measurement to be within 5% for absolute measurements and 2% when the comparative method is adapted.

Bereza et al. (2008) and Burov et al. (2006) are the only works, to our knowledge, that register radiation of two plane waves intersecting at an angle (Fig. 14). The theory of such interaction is extensively treated in Hamilton and Blackstock (1987) and Tjotta and Tjotta (1987). Just as for the collinear case, nonlinearity results in the generation of sum and difference frequency waves. However, in this case, energy is scattered outside the region of primary wave interaction (Fig. 14), where it is described by the Westervelt equation. This approach allows for the reconstruction of the frequency components of the B/A distribution that depend on the orientation of the two sources and the receiver, as well as the transmit frequencies. To increase the range of reconstructed frequencies and decrease the number of required transducer configurations, the authors transmit broadband signals. Moreover, these signals were encoded such that propagation delays for the coded signals were different and predictable in each coordinate of the medium. This way, each point scatterer radiated a specific coded signal proportional to β. The authors showed in silico and on ex vivo heterogeneous media (e.g., hog fat in water) that the high-frequency portion of B/A distribution can be reconstructed with only three transducers involved in the measurement (e.g., Fig. 14). In the case of multiple transducers where a sharp angle exists between two sources, the reconstruction of absolute β values is also possible. Besides this,

![FIG. 13. (Color online) Reprinted from Gong et al. (2004). (a) Model of the imaged media: porcine liver surrounded with porcine fat, submerged in water. (b) The acquired reflection-mode tomographic image, utilizing the parametric array method.](https://doi.org/10.1121/10.0003627)
the system is also capable of measuring the speed of sound \( c \) distribution with no additional measurements. Differently, this work registered the sum frequency, rather than the different frequency, since it allows for registration of a wider band of frequency components of \( \beta \) (Burov et al., 2006).

What is more, the registered signals contain information about the nonlinear parameter at a given location, unlike in the case of previous parametric array works and most FAM methods, which measure a cumulative signal.

Since the parametric array method allows generating frequencies much lower than the primary waves, most works based on Eqs. (46) and (47) neglect attenuation of the secondary waves \( x_s \). As demonstrated by Zhang et al. (2001a) and Zhang et al. (2001b), when using collinear beams, the difference frequency waves rise almost linearly with distance from the source, making it easier to account for diffraction effects. Moreover, the secondary beam has no side lobes. Despite these advantages, it has been noticed in Zheng et al. (1999) that “nearly 40 dB in amplitude level difference exists between the primary waves and their difference-frequency wave,” making the SNR level rather low and its practical application difficult. Varray (2011) noted that the length of the two transmitted pulses has to be sufficiently long for the generation of the secondary frequency components, setting a limitation to the resolution.

\[ c = c_0 + \frac{B}{2A} \frac{\Delta P}{\rho_0 c_0}. \] (48)

One can now see how the speed of sound \( c \) changes with excess pressure \( \Delta P \). Unlike in the thermodynamic method, Ichida et al. (1983) created a variation in pressure \( \Delta P \) by transmitting a high-power beam (pump wave) perpendicular to the probe beam [Fig. 15(a)], modifying the speed of sound \( c \) and, therefore, the phase of the probe beam. By registering the modified phase of the probe wave, they extracted \( B/A \) and created the very first images of the coefficient of nonlinearity in history.

The pumping wave techniques are presented hereafter in two sections: the classic pump wave technique and the SURF technique for echo-mode imaging. The main difference between these is that in the case of SURF, the probe wave has a much higher frequency than the pump wave. A summary of all the identified works is presented in Table VII. Note that pumping wave tomography corresponds to a line-by-line reconstruction, where the image is formed by translating the probe transmit and receive transducers along one direction [Fig. 15(a)]. This is different from conventional tomography used by FAM and the parametric array methods (Fig. 8).

### VII. PUMPING WAVES

Like the parametric array method, the pump wave method also exploits nonlinear effects produced when two plane waves interfere with each other. The principle of this technique is described best by the adiabatic dependence of speed of sound on \( B/A \) [Eq. (5)], already introduced for the thermodynamic method. Rearranging this equation with the use of the linear relation between pressure and particle velocity \( \Delta P = \rho_0 c_0 u \) (Hamilton and Blackstock, 1987), we obtain

![FIG. 14. (Color online) Schematic of the setup utilized in Burov et al. (2006), registering ultrasound scattered by two plane waves at an angle.](https://doi.org/10.1121/10.0003627)

**A. Classic pump wave technique**

In Ichida et al. (1983), the low power narrow carrier beam (named “probe” beam) was received by another transducer after its modulation by the high-power low-frequency plane wave, referred to as the pump wave [Fig. 15(a)]. The pump wave was sufficiently broad to insonify the entire object. This way, assuming a homogeneous density \( \rho_0 \) [Eq. (48)], \( B/A \) was the only parameter varying the speed of sound along the path of the probe beam. Figure 15(b) illustrates the modulated variations of the speed of sound \( \Delta c_1 \) and \( \Delta c_2 \) that the probe wave experiences as it propagates through a medium with the demonstrated \( B/A \) profile when pump waves \( P_{\text{transm}} \) and \( P_{\text{transm2}} \) of different frequencies were utilized, respectively. The authors showed that the phase shift \( \Delta \phi \) of the probe wave is the Fourier transform of the \( B/A \) distribution,

\[ \Delta \phi \left( \frac{1}{\lambda_p} \right) = \frac{1}{\pi} \frac{P_i}{\rho_0 c_0^2 \lambda_c} \int_0^L B/A(z) \exp(j2\pi/\lambda_p)dz, \] (49)

where \( z \) is the distance from the probe wave, \( \lambda_p \) and \( \lambda_c \) are the wavelengths of the pump and probe waves, correspondingly, \( P_i \) is the pump wave amplitude, and \( L \) is the distance the probe wave travelled in the studied medium. This way, the phase shift was measured for several frequencies transmitted by the pumping wave; the corresponding Fourier coefficients were then calculated and the \( B/A \) profile was reconstructed. Mechanical movement of the carrier probe allowed for generating a 2D image line by line. Interestingly, the authors of this work observed a high \( B/A \)
in muscle and bone, and low $B/A$ of fat, contrary to the results of more recent measurements.

The previous scheme “required considerable time” (Ichida et al., 1984) to acquire an image due to the frequency scanning of the pumping wave. A later modification (Ichida et al., 1984) of the sinusoidal pumping wave to an impulsive pumping wave, containing many frequency components at once, allowed this method to work in real-time.

In a further modification (Sato et al., 1985), the location of the pumping wave was moved opposite the probe beam, next to the probe receiver (Fig. 16), allowing for a more compact and practical system. This configuration reduced $B/A$ estimation errors due to distortion of the pumping wave’s front on the way to the probe beam due to inhomogeneous tissue attenuation. Moreover, another complementary acquisition where the probe and pump transducers

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**TABLE VII. Summary of works utilizing pumping waves to measure $B/A$.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Study</th>
<th>Type of assessment, imaged parameter</th>
<th>Investigated media</th>
<th>Uncert., %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic pump wave technique</td>
<td>Ichida et al., 1983</td>
<td>Homogeneous, tomography, $B/A$</td>
<td>Water; images of a fish, pig tissue in water, heated pig tissue</td>
<td>3 (liquid)</td>
</tr>
<tr>
<td></td>
<td>Ichida et al., 1984</td>
<td>Tomography, $B/A$</td>
<td>Liquid phantom with inclusions, human forearm</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Sato et al., 1985</td>
<td>Tomography, $\frac{B}{A}$</td>
<td>Liquid phantom with inclusions, in vivo hamster</td>
<td>—</td>
</tr>
<tr>
<td>Berkhout et al., 1991; Kim et al., 1990</td>
<td>In silico tomography</td>
<td></td>
<td>Heterogeneous phantoms of fluids, biological tissues</td>
<td>—</td>
</tr>
<tr>
<td>Cain, 1986</td>
<td></td>
<td>Theoretical basis of reflection-mode tomography, $B/A$</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Houshmand et al., 1988</td>
<td>In silico tomography, $B/A$</td>
<td>In silico phantoms with different 1D $B/A$ and attenuation profiles</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cain and Houshmand, 1989</td>
<td>In silico reflection-mode and transmit tomography, $B/A$</td>
<td>In silico phantoms with different 1D $B/A$ profiles in lossless and attenuative media</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kato and Watanabe, 1993, 1994</td>
<td>Homogeneous, heterogeneous 1D $B/A$ profiles</td>
<td>Water, benzyn alcohol layer in water</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SURF</td>
<td>Ueno et al., 1990</td>
<td>Echo-mode 2D imaging, temperature</td>
<td>Temperature distribution in pig tissue and human abdominal tumor</td>
<td>20 (tissue)</td>
</tr>
<tr>
<td>Fukakita et al., 1996</td>
<td>Echo-mode 1D imaging, $B/A$</td>
<td>Agar phantom, liquids, 2-layered liquid phantom</td>
<td>5 (liquid)</td>
<td></td>
</tr>
<tr>
<td>Kvam et al., 2019b</td>
<td>Echo-mode 2D imaging, $\beta_p = (1 + \frac{A}{A})k$</td>
<td>Phantom with inclusions</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
were interchanged allowed for tissue attenuation compensation. Together, all the mentioned studies performed by the same group have acquired B/A images of phantoms, fish, human arm, and a hamster in vivo (Ichida et al., 1983; Ichida et al., 1984; Sato et al., 1985).

Several further publications were devoted to improving the previously presented method in an in silico environment. Berkhout et al. (1991) and Kim et al. (1990) showed that by additionally registering the frequency modulation of the signal one could also reconstruct the imaginary part of the Fourier components of the B/A distribution. These complete Fourier components acquired for a specific set of wave numbers showed the superior quality of the B/A profile reconstruction. Cain (1986) presented the theoretical basis for real-time B/A imaging in reflection mode using only one transducer as a source of the probe wave, the pump wave, and a receiver. The proposed transmit pulse consisted of two parts: a unipolar, high-pressure pump pulse coming right after the single-frequency, sinusoids probe wave (Fig. 17). The probe wave's length equals twice the distance from the transducer to the reflector. This way, when the pump pulse is just released from the transducer, the leading edge of the probe wave is in the same position, already back at the transducer surface, encountering the unipolar pump pulse. As the waves propagate, the pump pulse continues to interact with the reflected probe wave, producing phase changes, in other locations of the sample. Houshmand et al. (1988) continued this work, and for the same configuration studied the quality of the B/A reconstruction when using different shapes of the pump pulse. Houshmand et al. (1988) showed that broadband pulses provide the best estimates of the coefficient of nonlinearity and that a chirp is a good option, providing a good B/A(z) estimate even for highly attenuating media. A following paper (Cain and Houshmand, 1989) focused on practical considerations suitable for both reflection and transmit modes: the limitations regarding pump width and pump amplitude as well as attenuation and distortion of the pump pulse as it propagates. The authors showed that compensation for the former effects is possible for several configurations of the pump and probe wave pulses, enabling satisfactory reconstruction of B/A profiles when a single reflector is present at the end of the image.

\[ \Delta \psi = \frac{\omega_p}{c_0} \int_0^L \left( \cos \theta + \frac{1}{2} \frac{B}{A}(z) \right) u_sdz, \]

where \( u_s \) and \( P_s \) the particle velocity and pressure of the pump wave, and \( \Delta \psi \) is the change in the probe wave’s speed of sound. The equation above reduces to Eq. (48) in the perpendicular configuration used by the first pump wave work (Ichida et al., 1983). For the plane wave case \( u_s = P_s/\rho_0 c_0 \), in the phase domain, we can derive

\[ \Delta \psi = \frac{\omega_p}{c_0} \int_0^L \left( \cos \theta + \frac{1}{2} \frac{B}{A}(z) \right) u_sdz, \]

where \( L \) is the interaction distance of the waves. Further, the authors showed that by registering the phase deviation of the probing wave \( \Delta \psi \) at intersection angles \( \theta = 0 \) and \( \theta = 180 \), they were able to reconstruct the distribution of absolute B/A(z) values for a path consisting of water and benzyl alcohol layers. Kato and Watanabe (1994) present the influence of diffraction effects on the B/A measurement. The system included two probe sources at opposite sides of the specimen, limiting the method to tomographic applications.

It was well noted by Kato and Watanabe (1993) that the pump wave method exhibited a rather large number of simulation studies (Berkhout et al., 1991; Cain, 1986; Cain and Houshmand, 1989; Houshmand et al., 1988; Kim et al., 1990), and not so many experimental works (Ichida et al., 1983; Ichida et al., 1984; Kato and Watanabe, 1993; Sato et al., 1985). The authors attributed this to rather small and difficult to measure phase changes induced by the pump pulse. A broad pump pulse is favorable for inducing stronger phase changes. However, it also decreases image resolution.
The current trade-off poses a requirement for an intense and stable pump source.

B. SURF technique for echo-mode imaging

SURF imaging can be seen as the successor of the pump wave method. The main difference is in that the probe wave has a much higher frequency than the pump wave (e.g., 2.5 MHz vs 300 kHz, Ueno et al., 1990) and is superimposed on the probe wave at a chosen phase interval. This requires a dual frequency source (Fukukita et al., 1996; Kvam et al., 2019b), where the probe wave transducer also acts as a receiver in echo-mode. This technique requires two acquisitions with different configurations of the pulse superposition. For example, in Figs. 18(a) and 18(b), the probe wave is superimposed on the pump wave at the zero crossing of the particle velocity and peak particle velocity, respectively. Given that the velocity at a point of an acoustic waveform can be expressed as (Fukukita et al., 1996; Kvam et al., 2019b; Muir and Carstensen, 1980)

\[
v = c_0 + \left( \frac{B}{2A} \right) \left( \frac{\Delta P}{\rho_0 c_0} \right) + u_p,
\]

where \( u_p \) is the particle velocity, a time delay \( \tau \) between the distorted and undistorted pump wave accumulates with

\[
\tau = L \left( \frac{1}{c_0} - \frac{1}{v} \right) = L \beta u_p / (c_0)^2,
\]

proportionally to the travelled distance \( L \) (Fig. 19). Therefore, the high-frequency probe pulse also distorts, undergoing either compression or expansion (depending on the phase of the pump wave), resulting in a shift of its center frequency. Moreover, the pump wave profile is affected by frequency-dependent attenuation, causing the center frequency of the pump wave to decrease with propagation. Fukukita et al. (1996) and Ueno et al. (1990) showed that \( B/A \) and \( z \) can be extracted from the ratio of the probe pulse spectra in two configurations of the probe wave superposition on the pump wave (Fig. 18). Moreover, since the frequencies of the detected probe pulses are close, the spectral ratio cancelled out scattering and diffraction effects. In their work, Fukukita et al. (1996) and Ueno et al. (1990) performed \( B/A \) and \( z \) measurements for several liquids, showing that \( B/A \) and \( z \) could be distinguished. In Ueno et al. (1990), in vivo images of the temperature distribution in pig tissue and a human abdominal tumor were inferred from measured \( B/A \) and attenuation. Unfortunately, no explicit images of \( B/A \) were provided.

Looking at Eq. (53) from another perspective, Kvam et al. (2019b) expressed \( v \) as

\[
v = c_0 \left( 1 + \left( 1 + \frac{B}{2A} \right) k_p P_s \right) = c_0 \left( 1 + \beta k_p P_s \right),
\]

substituting \( 1/A = k_s = 1/\rho_0 c_0^2 \), where \( k_s \) is the isentropic compressibility and \( \beta k_s = \beta_p \) is the nonlinear bulk elasticity of the medium. Since in a realistic clinical setting, the density \( \rho_0 \), the compressibility \( k_s \), and speed of sound \( c_0 \) are not known, the authors chose to measure the nonlinear bulk elasticity of the medium \( \beta_p \) rather than \( \beta \). Inferring it from time delays \( \tau \), they modified Eq. (53), describing the accumulated time delay \( \tau \) at point \( z_0 \),

\[
\tau(z_0) = \int_{z_0}^{0} \frac{\beta_p(z)}{c_0(z)} P_s(z) dz,
\]
for a plane wave probe pulse transmitted along $z$, superimposed with a positive phase of the pump wave, compared to that without a pump wave. The equation above neglects backward propagation delay and is accurate for the case when signals reflected from a single scatterer are compared. However, in reality, multiple scattering occurs as well as random interference, side lobes, reverberation noise, and refraction effects. Because of this, the authors chose not to infer the $\beta_p$ variation from the derivative of $\tau$ with respect to the receive time, which would amplify the variations, but rather fit a model based on Eq. (55) to estimate $\beta_p$. An image of the $\beta_p$ of a tissue-mimicking phantom is demonstrated in Fig. 20. The estimation required knowledge of the pump wave field in space $P(z)$, inferred from a measurement in a water tank.

Since the method compares signals with similar frequency content, it is considered relatively insensitive to attenuation and diffraction effects. The contribution of this work is significant since the method shows good contrast for an agar phantom with a corn oil inclusion in silico and in vitro, acquired with a linear 1D dual-frequency array. Besides this, Kvam et al. (2019a) found out that for most soft tissues the variability in $B/A$ comes from the isentropic compressibility $k_s = 1/A$.

**VIII. PHASE CONJUGATE BEAMS**

Phase conjugate beams are time reversed beams, reradiated back to the source (Cunningham et al., 2001) (Fig. 21). An optical image of a reradiated phase-conjugate beam was presented in Brysev et al. (2004). Phase conjugation provides the unique capability to compensate for phase distortion of the wave and achieves high-quality retrofocusing. Experimentally, this was demonstrated when a focused beam was transmitted through an aberration layer with random surface variations, and in a nonlinear nondispersive medium with inhomogeneities (Brysev et al., 2004; Preobrazhensky and Pernod, 2003). Since phase conjugation provides amplification to the selected harmonic component (e.g., fundamental and 2nd harmonic), 2nd harmonic generation occurs during backwards propagation, allowing to for the registration of the 2nd or 4th harmonic of the transmitted signal. The registered higher harmonic amplitudes reflect $B/A$, and when the system is mechanically moved, it can produce C-scans (Fig. 21). Following this strategy, imaging of isoechogenic phantoms with heterogeneous $B/A$ was proposed in Preobrazhensky and Pernod (2003), where the KZK equation was used to model wave propagation. Experimental images of isoechogenic liquid and liquid in gelatin phantoms (Krutyansky et al., 2007; Preobrazhensky et al., 2009) provided good contrast, reflecting the $B/A$ distribution when the 2nd and 4th harmonics were registered. The fundamental images reflected varying attenuation or reflection coefficients. No experimental images of tissues were acquired. Such a possibility remains unclear since retrofocusing has been demonstrated for the nonlinear modes

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**FIG. 20.** (Color online) (a) Schematic of an agar-based tissue-mimicking phantom with an inclusion filled with corn oil. (b) Reprinted from Kvam et al. (2019b). The image of the phantom acquired with the SURF method.

**FIG. 21.** (Color online) Typical phase conjugated beam setup. The arrows pointing to the right indicate the propagation of the originally transmitted signal; the arrows pointing to the left show the propagation of the phase conjugated beam.
only for nondispersive media (Preobrazhensky and Pernod, 2003). Diffraction effects can significantly deteriorate the quality of phase conjugation if the phase conjugator’s diameter is too small (Brysev et al., 2004).

IX. CONCLUSIONS

The first attempts to measure $B/A$ were made in the early 1960s, when the finite amplitude (Beyer, 1960; Shutilov, 1959) and thermodynamic methods (Beyer, 1960) were first proposed, almost simultaneously. The parametric array (Nakagawa et al., 1984) and the pump wave methods (Ichida et al., 1983) were developed next, making the method of aqueous solutions (Sarvazyan et al., 1990) and the phase conjugate method (Preobrazhensky and Pernod, 2003; Preobrazhensky et al., 2009) the last ones to emerge. Several papers were published, comparing the performance of some of these methods (Arnold et al., 1987; Law et al., 1983, 1985; Nakagawa et al., 1986; Zhang et al., 2001a).

Table VIII summarizes the main principle of $B/A$ measurement of all the techniques, their advantages and disadvantages, the reported range of uncertainties, and whether or not experimental $B/A$ images were acquired with the techniques. The latter possibility is particularly interesting from a clinical perspective since visualizing heterogeneous $B/A$ distributions gives us the opportunity to localize suspicious tissue regions. It is worth mentioning that the data about measurement accuracy in Table VIII is rather unbalanced since some methods were much more utilized and evaluated than others.

The main disadvantage of the thermodynamic method is in that it cannot be used for $B/A$ imaging and requires an advanced and complicated setup. At the same time, it is an accurate technique, which can be considered “the golden standard,” establishing a reference to evaluate all the other methods. The method of aqueous solutions is the only technique that is more accurate (Sarvazyan et al., 1990), but it requires a specific miniscule chamber and involves more complicated calculations and more extensive knowledge about the sample parameters. The work of Sarvazyan, in line with others (Sehgal et al., 1986b), indicated that $B/A$ reflects the strength of solute-solvent interactions, and grants information about molecule hydration. Moreover, Sarvazyan et al. (1990) observed that the replacement of an atomic group causes large changes in $B/A$ concentration increment. These observations, together with a small sample volume, make this method a powerful option for molecular studies of biological samples. The absence of such tests may be explained by inadequate alternatives currently applied in medicine, accurately detecting the chemical content of human fluids (Chen et al., 2008; Delanghe, 2007; Saatkamp et al., 2016). Most of these methods have difficulty distinguishing isomers (Chen et al., 2008), while $B/A$ is an excellent candidate for this task. Its utility for isomer distinction has already been demonstrated in Zhe et al. (2014) and may be of use when detecting early onset diabetes (Chen et al., 2008) and porphyria type (Kühnel et al., 1999).

In a situation when the pump wave and the probe wave propagate in the same direction, the parametric array method and pump wave method essentially merge (Cain et al., 1986). In this review, we allot the technique to the parametric array method if $B/A$ is inferred from the secondary wave pressure amplitude, and to the pump wave method when it is inferred through phase modulation of the probe wave. However, in the literature, this allocation may be different (e.g., SURF is regarded in Varay, 2011) as a parametric array method. Moreover, as FAM, the parametric array, and the pump wave methods all measure cumulative nonlinear effects of US propagation, in some papers (Kato and Watanabe, 1993; Varay et al., 2011a) all three are associated with one group, referred to as FAM. In order to avoid confusion, here we refer to these three groups of methods as the extended finite amplitude methods (EFAM) for convenience. Even though the phase conjugate beam method is also based on harmonic accumulation, it is to be treated separately.

The phase conjugate beam method is the most recent method, counting only a few works. Its great advantage resides in the automatic compensation for phase deviation caused by an inhomogeneous medium or irregular surface, characteristic of tissue. At the same time, it seems that phase conjugation is challenging for dissipative media like tissue, currently limiting this method to studies of liquid samples. Only qualitative characterization of the samples’ nonlinearity in conditions when the sample of interest has similar linear acoustic parameters as the reference medium, has been demonstrated at this point (Krutyansky et al., 2007; Preobrazhensky et al., 2009).

For all EFAMS, with few exceptions, attenuation measurement at the transmitted and received frequencies is strongly linked with $B/A$ measurement of a lossy medium. Another factor affecting wave propagation, and therefore relevant for all EFAMS, is diffraction. In transmit mode, the influence of diffraction can be mitigated by comparing the registered signal in the sample to that in a reference medium with a similar speed of sound, following the principle of the comparative method and the FAIS. Creative alternatives eliminating the need for diffraction correction also involve large source transducers (FAM) (Chavrier et al., 2006; Hunter et al., 2016; Jackson et al., 2014), or shifting of the diffraction pattern to the far field by attaching a steel delay line to the source (Wallace et al., 2007), or measurements in the extreme near (Law et al., 1981; Dunn et al., 1982) or far fields (Cortela et al., 2020; Dong et al., 1999; King et al., 2011). Since homogeneous EFAMS do not insonify the sample at high pressures, they can be suitable for in vitro assessment of organs for transplantation in transmission mode (e.g., liver in Hunter et al., 2016).

Of all EFAMs, FAM is the most extensive group with the largest number of subgroups and modifications. This is attributed to the method’s simplicity: it utilizes predominantly simple formulas within the framework of plane wave theory, and a simple setup with a source transmitting monochromatic signals. No composite waveforms (parametric
TABLE VIII. Summary of the main B/A measurement techniques. The graph Uncert., % states the range of errors identified in these groups of method. Looking at Tables III, IV, V, VI, VII one can identify the works, where these uncertainties were taken from. In some cases, if the accuracy was not stated, errors were derived based on either the reference values provided in the corresponding papers, or B/A measured with the thermodynamic technique. In many cases, no information about the errors was available since the actual B/A was not known (e.g., self-made phantom, B/A images of a hamster, fish, etc).

<table>
<thead>
<tr>
<th>Method</th>
<th>Main principle</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Uncert., %</th>
<th>Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional thermodynamic. Sec. IIIA</td>
<td>B/A is composed of 2 terms Proportional to the speed of sound Changes Δe induced by an isobaric Temperature change and isothermal Pressure change [Eq. (12)]</td>
<td>- Accurate, attenuation does not pose a big problem - Relatively insensitive to attenuation and diffraction effects</td>
<td>- Requires knowledge of the isobaric volume coefficient of thermal expansion q and the specific heat at constant pressure Cp</td>
<td>3 (liq), 5 (tis)</td>
<td>—</td>
</tr>
<tr>
<td>Isentropic thermodynamic. Sec. IIIB</td>
<td>B/A is proportional to the speed of sound changes Δc when pressure is varied adiabatically [Eq. (4)]</td>
<td>- Accurate, attenuation does not pose a big problem</td>
<td>- requires a complicated setup</td>
<td>0.85–4 (liq), 7 (tis)</td>
<td>—</td>
</tr>
<tr>
<td>Aqueous solutions. Sec. IV</td>
<td>Differential method, measuring the influence of small concentrations on B/A [Eq. (23)]</td>
<td>- Relatively insensitive to attenuation and diffraction effects</td>
<td>- Very specific, complicated setup</td>
<td>0.3 (liq)</td>
<td>—</td>
</tr>
<tr>
<td>Finite amplitude. Wave shape. Sec. V C</td>
<td>Determines B/A from the US wave shape</td>
<td>- More accurate compared to other FAM variations</td>
<td>- Light diffraction method: a complicated set up (A laser and an optical receiving system); - US equipment: transducer calibration and a broadband receiver required</td>
<td>7–8 (liq), 10 (tis)</td>
<td>—</td>
</tr>
<tr>
<td>Finite amplitude. Second harmonic measurements. Sec. VB</td>
<td>In most cases B/A is determined from formulas Based on the Fubini solution, modified to Incorporate losses and diffraction effects [Eqs. (26) – (30)]</td>
<td>- Relatively low accuracy</td>
<td>- In some cases, requires transducer calibration to estimate $P_1(0)$ - Diffraction and attenuation corrections</td>
<td>2–20 (liq),</td>
<td>Tomography (e.g., Fig. 9)</td>
</tr>
<tr>
<td>Finite amplitude. Fundamental non-linear absorption. Sec. VC</td>
<td>Determines B/A by measuring the fundamental saturation as source pressure is increased [Eqs. (42), (44)]</td>
<td>- Calibration is needed only at the fundamental frequency</td>
<td>- Transducer calibration required</td>
<td>10 (liq), 6 (ph)</td>
<td>Echo-mode imaging</td>
</tr>
<tr>
<td>Parametric array. Sec. VI</td>
<td>Measures the amplitude of the difference frequency wave that is proportional to B/A</td>
<td>- Produces narrow, collimated beams - The difference frequency beams have a low SNR</td>
<td></td>
<td>2–5 (liq), 10 (tis)</td>
<td>Tomography (e.g., Fig. 13)</td>
</tr>
</tbody>
</table>
array) or additional pump wave transducers, or composite transducers (pump wave) are needed to induce the nonlinear effects. All EFAMs enable B/A tomographic imaging (Table VIII). The first images were acquired with the pump wave method (Ichida et al., 1983), reconstructing the B/A profile line-by-line. Later, FAM and the parametric method were also used to obtain B/A images in transmit, based on multiple angle reconstruction tomography (Radon transform). Pump wave tomography, compared to the parametric array and FAM tomography, allows for independent B/A reconstruction along a single propagation line without the contribution of other directions. This approach can result in real-time tomography (Ichida et al., 1984) compared to reconstruction tomography. Exceptionally, Bereza et al. (2008) and Burov et al. (2006) are the only works (the parametric array method), where B/A values were mapped to their specific locations by signal encoding.

TABLE VIII. (Continued)

<table>
<thead>
<tr>
<th>Method</th>
<th>Main principle</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Uncert., %</th>
<th>Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic pump wave.</td>
<td>Registers the phase modulation of</td>
<td>- Influenced less by diffraction effects</td>
<td>- The length of source pulses has to be sufficiently long to generate secondary components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sec. VII A</td>
<td>The probe wave by the pump wave</td>
<td>from phase modulation rather than pressure units</td>
<td>- In practice, requires a separate pump transducer</td>
<td>3 (liq)</td>
<td>Tomography</td>
</tr>
<tr>
<td>Pump wave, SURF.</td>
<td>Registers the frequency shift or the time</td>
<td>- No diffraction correction needed</td>
<td>- In practice, requires a dual frequency transducer</td>
<td>5 (liq), 20 (tis)</td>
<td>Echo-mode imaging (e.g., Fig. 20)</td>
</tr>
<tr>
<td>Sec. VII B</td>
<td>Delay of the probe wave in two pulse configurations</td>
<td>- Able to measure attenuation simultaneously</td>
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<tr>
<td>Phase conjugate beams.</td>
<td>Determines B/A from higher harmonic amplitudes of the phase conjugated beam</td>
<td>- Compensates for phase distortion (automatic retrofocusing)</td>
<td>- Reflects qualitative B/A values</td>
<td>—</td>
<td>C-scans</td>
</tr>
<tr>
<td>Sec. VIII</td>
<td>The phase conjugator amplifies the signal</td>
<td>- Only for nondissipative/weakly dissipative media</td>
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</table>

array) or additional pump wave transducers, or composite transducers (pump wave) are needed to induce the nonlinear effects. All EFAMs enable B/A tomographic imaging (Table VIII). The first images were acquired with the pump wave method (Ichida et al., 1983), reconstructing the B/A profile line-by-line. Later, FAM and the parametric method were also used to obtain B/A images in transmit, based on multiple angle reconstruction tomography (Radon transform). Pump wave tomography, compared to the parametric array and FAM tomography, allows for independent B/A reconstruction along a single propagation line without the contribution of other directions. This approach can result in real-time tomography (Ichida et al., 1984) compared to reconstruction tomography. At the same time, reconstruction tomography allows improving the image resolution and quality due to numerous projections involved in the reconstruction process (Caponnetto and Bertero, 1997). Parametric array tomography allows for better resolution compared to FAM tomography (see Figs. 13 and 9) since the generated beams at the sum and difference frequencies are narrower compared to the second harmonic beam (Gong et al., 2004; Wang et al., 2003; Zhang et al., 2001a). As for pump wave tomography, the image resolution is defined by the frequency of the pump wave and the size of the probe beam (Sato et al., 1985). This way, we expect the resolution of pump wave tomography to be lower than for the parametric array and FAM methods since the probe beam is formed by the transmitted fundamental component with a wider beam. Discrimination between healthy (B/A = 6.9) and diseased liver (B/A = 8.3) has been achieved with parametric array and FAM tomography (Gong et al., 2004), with even better image contrast for healthy liver and fat (Figs. 13 and 9). Unfortunately, all the pump wave tomographic works that we were able to identify showed rather poor quality images dating from 1983 to 1985 (Ichida et al., 1983; Sato et al., 1985). Therefore, it was difficult to compare pump wave tomography to the other types of tomography in this respect. Being a valuable asset, tomography still limits the exam to specific organs, such as the breast, and is rather time consuming for reconstruction. Paving the way for echo-mode imaging, several works have been devoted to reflection mode tomography, detecting the signals from a strong reflector on the side of the medium opposite from the source-receiver transducer (e.g., Cain, 1986; Gong et al., 2004; Wang et al., 2003). However, this resulted in little improvement with respect to B/A’s clinical applications.

Development to echo-mode imaging faced important challenges since the scatterer density distribution and echogenicity are the dominating factors influencing the strength of the reflected signal. Therefore, all echo-mode images were generated by limiting the scatterer effect by
normalizing or comparing the signal of interest to a reference signal, assumed to have a similar scattering pattern. This strategy also has the benefit of mitigating diffraction and attenuation effects. Another common assumption in the echo-mode works is that the nonlinear effect in backwards propagation is neglected since the amplitude of the reflected echoes is small compared to the forward propagating beam pressure (only for tissue, e.g., not solids). B/A echo-mode imaging was implemented with FAM, 2nd harmonic measurements (Akiyama, 2000; Fujii et al., 2004; Gong et al., 2004; Liu et al., 2008; Toulemonde et al., 2015; van Sloun et al., 2015; Varray et al., 2011b), Fundamental nonlinear absorption (Fatemi and Greenleaf, 1996; Nikoonahad and Liu, 1989, 1990) and SURF of the pump wave method (Fukukita et al., 1987, 1996; Kvam et al., 2019b) for assessment of the B/A depth profile of tissue or tissue-mimicking phantoms in echo-mode are Fatemi and Greenleaf (1996), Kvam et al. (2019b), Toulemonde et al. (2015), van Sloun et al. (2015), and Varray et al. (2011b).

The limited number of works presenting the B/A depth profile of tissue in their images points to the observation that even the normalized signals, corrected for scatterer effects, show to be nevertheless noisy (e.g., in Fujii et al., 2004; Toulemonde et al., 2014). Tissue, being a structure full of point scatterers located close together, favors interference of scattered signals and multiple scattering (Aubry and Derode, 2011), adding to the effects of grating lobes, reverberation noise (Kremkau and Taylor, 1986), and electronic noise. Many presented approaches (Akiyama, 2000; Fujii et al., 2004; Gong et al., 2004; Liu et al., 2008; van Sloun et al., 2015; Varray et al., 2011b) for assessment of the B/A depth profile involve differentiation of the normalized signal with respect to time or space, amplifying the noise. Differently, Kvam et al. (2019b) formulated an optimization problem, based on the expression of the measured time delay \( \tau \), introducing penalties on the modelled process. Table IX shows that the only works able to assess the in-depth profile of B/A (or of a proportional parameter) of tissue or tissue-mimicking phantoms in echo-mode are Fatemi and Greenleaf (1996), Kvam et al. (2019b), Toulemonde et al. (2015), van Sloun et al. (2015), and Varray et al. (2011b). These demonstrate that current echo-mode imaging permits the delineation of tissue-mimicking phantom regions with different oil content/contrast agent content (Kvam et al., 2019b; Toulemonde et al., 2015; van Sloun et al., 2015; Varray et al., 2011b). Fatemi and Greenleaf (1996) were the only ones who performed B/A echo-mode imaging of heterogeneous tissues, where shadowing reflected the parameter of the nonlinearity of the preceding regions. Echo-mode in-depth temperature profiles in tissue, inferred from B/A, have been demonstrated only in Ueno et al. (1990).

Interestingly, some debate regarding the utility of B/A for temperature monitoring still exists, with certain studies showing a small B/A increment when tissue is coagulated (Jackson et al., 2014; Saito and Kim, 2011), and others stating the contrary (Choi et al., 2011; Lu et al., 2004). Moreover, from another perspective, Gong et al. (2004) and

**TABLE IX. Summary of the echo-mode methods implemented experimentally.**

<table>
<thead>
<tr>
<th>Method</th>
<th>Reference signal</th>
<th>Studied media</th>
<th>Probe</th>
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<tr>
<td>FAM. 2nd Harmonic measurements</td>
<td>- Fundamental at two harmonic frequency ( 2f_0 ) (Akiyama, 2000; Fujii et al., 2004; Gong et al., 2004; Liu et al., 2008)</td>
<td>- Homogeneous liquids and homogenous bovine liver (Akiyama, 2000), - Homogeneous in vivo human liver (Fujii et al., 2004)</td>
<td>- Sector array transducer (Fujii et al., 2004)</td>
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<td>- Fundamental at ( f_0 ) (van Sloun et al., 2015)</td>
<td>- Homogeneous tissue (Gong et al., 2004; Liu et al., 2008)</td>
<td>- Compound piezoelectric transducer (Gong et al., 2004; Liu et al., 2008)</td>
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<td></td>
<td>- Tissue-mimicking phantom with two layers</td>
<td>- Two transducers (Akiyama, 2000)</td>
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<td></td>
<td>- 2nd harmonic in a reference medium (Varray et al., 2011b)</td>
<td>- Esaote LA332 commercial probe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Two tissue-mimicking phantoms: with an inclusion and with a contrast-agent filled cavity</td>
<td>- Clinical probe</td>
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<tr>
<td>FAM. Fundamental nonlinear absorption</td>
<td>- Fundamental at ( f_0 ) and 2nd harmonic in a reference medium (Toulemonde et al., 2014, 2015)</td>
<td>- Tissue-mimicking phantom with three layers</td>
<td>- Commercial Acuson linear array probe</td>
</tr>
<tr>
<td>Pumping waves, SURF</td>
<td>- Low amplitude signal at the same frequency</td>
<td>- Liquid layers (Nikoonahad and Liu, 1989)</td>
<td>- Dual frequency probe of 2 circular transducers (Fukukita et al., 1996)</td>
</tr>
<tr>
<td></td>
<td>The probe pulse superimposed at another phase of the pump wave</td>
<td>- Liquid layers and in vitro heterogeneous tissue (Fatemi and Greenleaf, 1996)</td>
<td>- Dual-frequency linear array (Kvam et al., 2019b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Agar phantom with inclusion (Kvam et al., 2019b)</td>
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*The word “homogeneous” in this table refers to the assumption of homogeneity in depth. These studies presented B/A images that were acquired by mechanical movement of the probe.*
Gong et al. (1993) demonstrated that B/A was able to provide better discrimination of porcine liver tissue compared to attenuation, velocity $c_0$, and density $\rho_0$, while Kvam et al. (2019a) concluded that for many soft tissues most of the estimated variability in B/A comes from variability in $1/A = \rho_0 c_0$. These controversial results indicate that more research is required to identify the boundaries of B/A applicability. Moreover, in our view, the utility of the thermodynamic technique and especially of the method for aqueous solutions may have been overlooked in biochemistry, molecular physics, and possible human fluid sample tests. Even though B/A cannot be used to determine the accurate and detailed chemical content of a substance, it is sensitive to structural change. Therefore, it would be particularly useful for the assessment of structural changes of the same substance (Zhe et al., 2014) and has potential to diagnose diseases (Chen et al., 2008; Kühnel et al., 1999) through identification of the isomer type in human fluids.

This review brings us to the conclusion that more research is required to reformulate the boundaries of B/A applicability, possibly dispelling some current hopes for clinical applications and bringing new opportunities. The thermodynamic technique and the method for aqueous solutions are the most accurate, the latter being especially useful for studies of small solute concentrations. Transmission mode EFAMS allow less accurate B/A estimation, but with a simpler setup and wider perspective clinical applications. They can be of use when assessing the condition of transplantation organs (Hunter et al., 2016), or measuring B/A in vivo as a uniform parameter (Fujii et al., 2004). All EFAMS enable transmit tomography, limiting the exam to only a few clinical applications such as breast imaging. Development of an ultrasound B/A imaging modality is greatly hindered due to the fact that in echo-mode, the strength of the reflected signal is to a greater extent defined by the scatterer distribution and the variation of linear ultrasound parameters ($c_0, \rho_0$) than by B/A. Besides this, accurate imaging requires correction for diffusion effects, attenuation, various noise artifacts, and interference of signals coming from tissue scatterers. Strategies eliminating these effects would pave the way to B/A imaging in the clinic. Moreover, they may open new possibilities for imaging of the third-order nonlinear parameter C/A (Burov et al., 2015; Burov et al., 2013; Liu et al., 2007; Xu et al., 2003).

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