Modeling ultrasound propagation through material of increasing geometrical complexity

Maryam Odabaee, Mostafa Odabaee, Matthew Pelekanos, Gerhard Leinenga, Jürgen Götz

Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, St Lucia Campus, Brisbane, QLD 4072, Australia

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ABSTRACT

Ultrasound is increasingly being recognized as a neuromodulatory and therapeutic tool, inducing a broad range of bio-effects in the tissue of experimental animals and humans. To achieve these effects in a predictable manner in the human brain, the thick cancellous skull presents a problem, causing attenuation. In order to overcome this challenge, as a first step, the acoustic properties of a set of simple bone-modeling resin samples that displayed an increased geometrical complexity (increasing step sizes) were analyzed. Using two Non-Destructive Testing (NDT) transducers, we found that Wiener deconvolution predicted the Ultrasound Acoustic Response (UAR) and attenuation caused by the samples. However, whereas the UAR of samples with step sizes larger than the wavelength could be accurately estimated, the prediction was not accurate when the sample had a smaller step size. Furthermore, a Finite Element Analysis (FEA) performed in ANSYS determined that the scattering and refraction of sound waves was significantly higher in complex samples with smaller step sizes compared to simple samples with a larger step size. Together, these reveals an interaction of frequency and geometrical complexity in predicting the UAR and attenuation. These findings could in future be applied to poro-visco-elastic materials that better model the human skull.

1. Introduction

Ultrasound is increasingly being explored as a therapeutic modality for diseases of the brain [1]. Established applications in peripheral tissue include lithotripsy and physiotherapy, whereas emerging applications for the brain include tissue ablation by inducing hyperthermia, for example to treat essential tremor [2], and microbubble-facilitated opening of the blood–brain barrier (BBB) to deliver drugs past the BBB as exemplified by anti-cancer antibodies in the treatment of gliomas [3]. We and others have shown in transgenic mouse models that microbubble-mediated opening of the BBB with ultrasound is also an efficient method to reduce two key pathologies of Alzheimer’s disease [4–8], and that treating wild-type mice with ultrasound is safe long-term [9]. In a subset of these studies, cognitive impairment was reversed and ultrasound on its own, without delivery of a therapeutic agent, was able to achieve therapeutic outcomes. Safety studies have also been performed in larger animals including beagles [10], sheep [11] and macaques [12]. Together, these results have prompted clinical trials in humans.

However, applying the principles established in mice to larger animals is not simply a matter of scaling up; ultrasound is also affected by the human skull, that different from mice, consists of two outer layers and a central spongy cancellous bone (diploë) with liquid-filled pores, which cause ultrasound to be reflected by the layer boundaries and pores and absorbed by the skull, resulting in a significant temperature increase in the bone [13,14]. As a consequence, insufficient energy is transmitted into the brain. Magnetic resonance imaging (MRI) and computed tomography (CT) has been instrumental in determining both the profile and internal structure of the skull [15].

In order to overcome the skull and determine its acoustic properties, a stepwise approach of modeling is required. In the current study, we modeled the human skull bone by simple resin samples with a bone-like density and a defined geometry in order to predict wave propagation and determine their acoustic properties using a signal processing approach. This allows simulating the process in a system of building blocks that produce a clear illustration of sample behavior towards ultrasonic waves, termed Ultrasound Acoustic Response (UAR). Based on previous work by Langton and colleagues, the initial assumption was made that the waveform shows a linear behavior as it passes along different paths through the samples [16]. However, we found that such a linear behavior is not applicable when the complexity of the sample’s geometry increases. Moreover, a Finite Element Analysis (FEA) was performed to investigate ultrasound refraction and scattering that affects the direction of wave propagating, an analysis not possible by...
UAR. Together, this serves as a foundation for follow-up studies using layered and poro-visco-elastic models (that more faithfully represent the human skull) and human skulls.

2. Methods

2.1. 3D printing of step samples

A series of full and partial cylindrical samples was generated with a 50 μm resolution 3D printer (Kudo3D, Titan1, Kudo3D, Pleasanton, California, United States, www.kudo3d.com) using resin (ultrasound velocity was measured as 2200 m/s, 3DM-ABS, 3D-Materials, Feldkirch, France). Seven samples (b) to (h) with increasing complexity were generated using water (sample (a)) as reference (Fig. 1a). The simplest sample (b) comprised a cylinder of 20 mm length and 25.4 mm diameter covering the surface of the active transducer elements fully. The other samples were designed with equal step heights. As illustrated for the 3-step sample (close-up), the path length of the acoustic wave in the second and third step is 2 and 3 times that of the first step, respectively. A similar principle applies to the other samples (ranging from the 2 to 20 steps), with the steps varying in length and size (Table 1).

2.2. Ultrasonic testbed and data acquisition platform

The acoustic setup consisted of a pair of single-element transducers (Olympus Immersion Transducer, 1-inch (25.4 mm) diameter, with 0.5,
1, and 2.25 MHz center frequencies, cat# v301-su, c302-su, and c304-sc, respectively), used as transmitter and receiver in a through-transmission mode (Fig. 1b). The body and connections of the transducers were covered with Parafilm and placed in a Perspex water tank (10 mm thick, internal dimensions 40 cm × 30 cm × 25 cm) using a holder (Newport Linear Stage) mounted on a 250 mm × 300 mm solid aluminum breadboard to obtain a stable mounting platform at the base of the tank, to accommodate and coaxially align the sample and transducers. Then the tank was filled with degassed water and the sample and transducers were submerged (Fig. 1c).

The following equipment was used (Fig. 1c): A waveform generator (Agilent Trueform, Keysight 33512B, frequency range of 1 Hz to 20 MHz, with arbitrary waveform capabilities), was used to produce 100 mV signals consisting of bursts of sinusoids, with frequencies of 0.5, 1 and 2.25 MHz. A broadband power amplifier (Electronics & Innovation, 240L) increased the power of the signal by 50 dB. The receiver

<table>
<thead>
<tr>
<th>Sample</th>
<th>Number of steps</th>
<th>Step length (mm)</th>
<th>Step size (height) (mm)</th>
</tr>
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<tbody>
<tr>
<td>(b)</td>
<td>1</td>
<td>20</td>
<td>25.4</td>
</tr>
<tr>
<td>(c)</td>
<td>2</td>
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<td>(d)</td>
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<tr>
<td>(h)</td>
<td>20</td>
<td>1</td>
<td>1.27</td>
</tr>
</tbody>
</table>

Table 1
Dimension of resin samples with a length of 20 mm and a diameter of 25.4 mm.

Fig. 2. UAR modeling and validation. (a) Functional block diagram calculating the UAR. (b) Using the 3-step sample (d), the input signal is shown (in back) and the receiver signal in response to an ultrasonic excitation by the wave generator (in green). (c) Simulation of waveform propagation through this sample using MATLAB Simulink, showing the input and output signal generated by the simulation. (d) The applied input signal in the simulated model is shown in black, and the generated output signal in green. (e) Comparison of the experimental and simulated UAR data for the 3-step sample (d) validates the simulation efforts.
transducer was connected to an ultrasonic pre-amplifier with a gain of 34 dB (Olympus 5562). The amplified received signal was sent to the data acquisition platform, which included a 16-bit high speed digitizer with 250 MS/s and 14 bit resolution (Spectrum, M4i platform), supported by the SBench 6 software (Spectrum http://spectrum-instrumentation.com/en/sbench-6-overview). A commercial software package (MATLAB 9.0, The MathWorks Inc., Natick, MA, 2000, United States) was applied and drivers provided by Spectrum were used to continuously access and record data from the digitizer.

In the testbed, the samples were placed and aligned in front of the transmitter transducer such that the back (full face) of the sample was attached to the transducer. On its way to the receiver transducer, different combinations of paths were encountered with resin as the solid and water as the liquid part, with each path having its unique acoustic properties. For example, in the 2-step sample (c) (Fig. 1a), there are two paths that the wave passes through. The first path consists of 10 mm solid resin and 10 mm water (first step), and the second path only of 20 mm resin (second step). This means that the wave faces different delays and attenuations due to the different acoustic properties of the paths. To perform acoustic measurements and validate the 2D FEA, an Onda AIMS III tank (Onda, Sunnyvale, USA) equipped with a calibrated needle hydrophone (HNR-500, Onda) and a 20 dB preamplifier (AH-2010, Onda) was used (Fig. 1d).

2.3. Signal processing approach

To determine the acoustic properties of the samples, the process was simulated in a system of building blocks that produced a clear illustration of sample behavior linearly towards ultrasonic waves, termed UAR.

The analysis of the captured data was done in two stages. In the first stage, the equipment, sample and broadband power amplifier up to the ultrasonic pre-amplifier were treated as a single system. Accordingly, the input to this system was the electrical signal, generated by the signal generator, and the output was the signal received by the data acquisition platform (Fig. 1). We applied deconvolution to these signals to estimate the UAR as the system’s response to the ultrasonic signal. In the second stage, the above system was modeled in Simulink in MATLAB. An example of such a modeling is shown using sample (d). The recorded input signal of the experiment was used as the input of the model, and the output was generated in the simulation and stored. Similar to what was done in the experiment for the input signal, deconvolution was applied to these signals to calculate the UAR of the model. Finally, the UAR of the simulation and the experiment were compared (Fig. 2).

We assumed that the total procedure of ultrasonic system can be explained as a Linear Time Invariant (LTI) system [17].

An LTI system can be completely identified in time by its input/output relationship. To extend the LTI concept to the acoustic wave experiments, UAR was used to describe the transfer function of the system. It can be expressed by using the convolution operator as:

\[
y[n] = x[n] * h[n] = \sum_{k=-\infty}^{\infty} x[k]h[n-k]
\]

(1)

where \(x[n]\) is the sampled input signal and \(y[n]\) is the sampled output signal in the data acquisition platform. \(\ast\) is the discrete convolution operator, and \(h[n]\) represents the discrete transfer function or UAR of the system.

The inverse operation, deconvolution which is calculating \(h[n]\) given \(x[n]\) and \(y[n]\), cannot be achieved by using a single inverse operator. However, theoretically it is possible to find \(h(n)\) using

\[
h[n] = \mathcal{F}^{-1}\left\{ \frac{Y[k]}{X[k]} \right\}
\]

(2)
in which \(\mathcal{F}^{-1}\) represents the inverse discrete Fourier transform and \(X[k]\), and \(Y[k]\) is the discrete Fourier transform of \(x[n]\) and \(y[n]\), respectively. In practical terms, due to the perpetual presence of thermal and electrical noise intrinsic to the system, calculating \(h[n]\) using the above equation is almost impossible. \(v[n]\) is the additive noise assumed to be uncorrelated with the input:

\[
y[n] = x[n] * h[n] + v[n]
\]

(3)

Since noise is a random signal, it is impossible to directly calculate \(h[n]\) by a simple deconvolution method (Eq. (2)).

More generally, there are various deconvolution methods available [18,19]. For ultrasound, Wiener Filtering, Spectral Extrapolation, Minimum Variance Deconvolution (MVD), Curve Fitting Methods L1 and L2 [18,20], and the Active-set method have been used [21]. Wiener filtering can preserve most of the information associated with signals at regions of high signal-to-noise ratios in the frequency domain. This filter can also be applied to the problem of noise reduction [22]. Furthermore, when the power spectrum of the input \(X[k]\), noise \(v[k]\), plus the frequency response of the system, \(h[n]\), are known, the mean squared error is minimized when the Wiener filter is used for deconvolution [23]. Wiener filtering has been applied to ultrasonic NDT and found to have advantages over other deconvolution methods reported [20].

The Wiener filtering assumes that additive noise is present along with the system’s output and uses the following equation to estimate \(h[n]\)

\[
\hat{h}[n] = \mathcal{F}^{-1}\left(\frac{X[k]Y[k]}{|X[k]|^2 + q}\right)
\]

(4)
in which \(|X[k]|^2\) is the complex conjugate of \(X[k]\) and \(q\) is called the noise desensitizing factor. The \(q\) factor is a function of the frequency which can be estimated based on the power spectral densities of additive noise and the unknown impulse response \(h[n]\). Estimation of these densities is not trivial. The \(q\) factor is assumed to be constant amounting to 1% of the maximum of the squared magnitude spectrum of the input signal \(|X[k]|^2\) [18,20].

It is important to note that the UAR of the above acoustic test system, \(\hat{h}[n]\), does not only include the that of the sample, but also that of the entire equipment and all components of the test bed (Fig. 1b). Accordingly, Eq. (3) reflects the internal components of the total system

\[
y[n] = x[n] * (h_1[n] * h_3[n] * h_4[n]) + v[n]
\]

(5)

and

\[
h[n] = h_1[n] * h_3[n] * h_4[n]
\]

where \(h_1\), \(h_3\), \(h_4\) are the UAR of the power amplifier-to-transmitter transducer, the sample, and the receiver transducer-to-pre-amp, respectively (Fig. 1b). This necessitates having responses and mutual signal/impedance matching and transfer ratios for all of these parts. In terms of the above equation (Eq. (5)), the aim was to find \(h_1\), i.e. the UAR of the sample, while the estimated UAR, \(\hat{h}\), includes other unknown parameters, \(\hat{h}_1\) and \(\hat{h}_3\). To address this problem, using the commutative property of the convolution relationship, the effects of the UAR of the sample and equipment were separated as

\[
\hat{h}[n] = \hat{h}_3[n] * \hat{h}_1[n] * \hat{h}_2[n]
\]

(6)

and

\[
\hat{h}_{3,1} \neq \hat{h}_3[n] * \hat{h}_1[n]
\]

after substituting

\[
\hat{h}[n] = \hat{h}_{3,1}[n] * \hat{h}_2[n]
\]

in which \(\hat{h}_{3,1}\) represents the response of the system when there is no sample between the two transducers. Rewriting Eq. (5) and replacing \(\hat{h}[n]\) by its equivalent value from Eq. (6) will give

\[
y[n] = (x[n] * \hat{h}_{3,1}[n]) * \hat{h}_2[n] + v[n]
\]

(7)
Then the output signal in the no-sample configuration can be shown as
\[ y_{1,3}[n] = x[n] + h_{1,3} \]  
Replacing \( x[n] \) with \( h_{1,3} \) in Eq. (7) by \( y_{1,3}[n] \) will result in
\[ y[n] = y_{1,3}[n] + h_{2} + v[n] \] (9)
This indicates that the output of the system (that includes the equipment and sample), i.e. \( y[n] \), can equally be generated by a system consisting only of the sample, when the input is the signal \( y_{1,3}[n] \). The Eq. (9) indicates when signals \( y[n] \) and \( y_{1,3}[n] \) are known, \( h_{2} \), by applying Wiener deconvolution in a similar manner to Eq. (4), can be estimated as follows:
\[ \hat{h}_{2}[n] = \mathcal{F}^{-1} \left( \frac{Y_{1,3}[k] Y[k]^*}{|Y[k]|^2 + q} \right) \] (10)
where \( Y_{1,3}[k] \) represents the Fourier transform of \( y_{1,3}[n] \), i.e. the output when transmitter and receiver transducer are attached together when no other experiment condition is changed, and \( Y[k] \) is the complex conjugate of \( Y[k] \). Subsequently, an experiment using no sample (i.e. attaching transmitter and receiver transducers without spacing) was performed, and the output, i.e. \( y_{1,3}[n] \) was recorded. This signal was used as the input signal in both the simulation and the experiment in order to find \( h_{2}[n] \), i.e. the UAR of the sample.

In the second stage, samples were modeled with Simulink. The main assumption was a linear behavior of acoustic waves through samples and that each step of the complex multi-step samples acts as a separate aperture for the wave front. Hence, it was possible to consider the part of the wave front that passes through this aperture as a separate sonic wave and to sum up the effects of all wave fronts arriving at the receiver transducer through the various steps. In such a scenario, each sonic wave experiences a separate path that might be different because of the differences in resin and water composition. Consequently, each wave has a different average speed and average attenuations for the entire path. Therefore, multiple versions of the initial wave arrive at the receiver transducer, with different delays and attenuations, constituting the received waveform. Another assumption is that for each path the wave in the sample propagates in the same sender-to-receiver direction, perpendicular to the face of the receiver transducer, and therefore, wave scattering and reflection could be neglected.

By assuming the quasi-plane waves for the ultrasound waves incident to the solid – liquid boundary, the experimental setup can be reduced to the Thompson-Gray measurement model in which the entire ultrasonic system can be seen as a series of consecutive LTI components with each performing a single modification of the delay, attenuation and transmission coefficient blocks. Simulink is a block diagram environment for simulation and model-based design that is integrated into MATLAB enabling to incorporate various analytical equations in the form of blocks. In order to simplify the verification of separate wave path assumption through each step, the wave propagation phenomena such as diffraction, and scattering have not been considered in this approach and the simulation of the experiments were performed using four Simulink blocks implementing four major modifications:

- **Attenuation block**: Designed to model the energy lost due to scattering, refraction and absorption in the medium [17]. The amplitude of ultrasound signal traveling through a material is used to calculate the attenuation magnitude as
\[ I = I_0 e^{-\alpha x} \] (11)
in which \( I_0 \) is the input ultrasound signal, \( \alpha \) the attenuation coefficient and \( x \) the path length in the medium. The attenuation coefficient, \( \alpha \) [Neper/cm], was determined by measuring the reduction in amplitude of an ultrasonic wave which has traveled through a material:
\[ \alpha = -\frac{1}{x} \ln \frac{I}{I_0} \] (12)
Since water has a low attenuation in the acoustic field its contribution can be neglected, and it can be considered as a reference signal to calculate the attenuation of the resin samples. The attenuation coefficients for resin and water were calculated (with the conversion of the dB-scale: \( dB = 20 \ln(e) \)) and applied in the simulation model (Table 2).

<table>
<thead>
<tr>
<th>Frequency (MHz)</th>
<th>Attenuation (dB/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2.25</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Then the output signal magnitude in the no-sample configuration can be shown as
\[ y_{1,3}[n] = x[n] + h_{1,3} \] (8)

- **Delay block**: Represents the delay when passing through a medium. It is calculated based on the speed of sound and the distance that the wave propagates in the medium as
\[ t_{\text{delay}} = \frac{x}{V_C} \] (13)
in which \( x \) represents the length of the sample (for each step) and \( V_C \) the speed of sound in the sample that was experimentally determined.

- **Transmission coefficient block**: Whenever there are impediments or abrupt changes in the path of an acoustic wave in a medium, part of the wave is reflected back. In an environment with differences in acoustic impedance, wave reflection happens and reflection and transmission coefficients for the plane wave and planar incidence plane, as per our assumptions, are given by [24]:
\[ T_{1,2} = \frac{2Z_2}{Z_1 + Z_2} \]
\[ R_{1,2} = \frac{Z_1 - Z_2}{Z_1 + Z_2} \] (14)
where \( T_{1,2} \) and \( R_{1,2} \) are the wave transmission and reflection coefficients, respectively, for an interface going from medium with impedance \( Z_1 \) to a medium with impedance \( Z_2 \). The following equation is applied to find impedances for the calculation of the transmission coefficients
\[ Z = \rho V_C \] (15)
in which \( \rho \) is the medium density and \( V_C \) is the acoustic velocity in the medium. Based on the measured density and speed of sound of 1162.55 kg/m 3 and 2200 m/s for resin and 1000 kg/m 3 and 1509 m/s for water, respectively, transmission and reflection ratios were obtained as 0.7421 and 0.2579, respectively. The effect of the reflected waves, which reflect back to the transmitter and back again to the receiver, due to the small reflection ratios, was negligible in the experiments (and hence in the simulations).

- **Area factor block**: Since it is assumed that each step of the multi-step samples acts as a separate aperture for the wave front, the size of the aperture is another parameter that affects the transmitted acoustic power through each path. To obtain the area of the segment of the circle that constitutes that path, the front face of each step is divided by the area of the sample’s face (the whole circle). For a circle of a radius \( R \), the area of a segment of the height \( h \) is given:
\[ A = \frac{R^2(\pi - \sin \theta)}{2} \] (16)
where the angle \( \theta \) is given by
\[ \theta = \arccos \left( \frac{R-h}{R} \right) \] (17)
The value of the area factor is a fraction that is then multiplied by the amplitude of the signal.

- **Other general blocks:** Input, Add for summation and Scope for displaying the output. These are routinely used in Simulink and no specific implementation is applied. For instance, the input block uses the files of the saved measurements, although it is possible to apply any type of input.

Accordingly, considering a linear behavior of the wave through the sample and negligible scattering and refraction effects, each wave front going through a sample can be separated into different paths. For instance, simulation of sample ‘d’ (Fig. 2b), generates three separate paths. The first path, the bottom step, contains 20 mm of resin material. Accordingly, this path is modeled as a Resin delay block, a Resin attenuation block and an Area factor block (equal to the area of the first step) (Fig. 2b, top row). The second path goes through the middle step containing resin and water with an interface between both materials at 13.33 mm from the beginning of the path. Thus, this path is simulated as a Resin delay block, a Resin attenuation block, a Transmission coefficient block, a Water delay block, a Water attenuation block and an Area factor block (Fig. 2b, second row). Finally, the third path of the wave, containing an interface of resin and water at a length of 6.66 mm, is similar to the second row, except for the values for the delay and attenuation blocks (Fig. 2b, bottom row). The output signals of the three paths are added up and sent to the output (scope). Using the LTI concept, we performed a simulation with Simulink that aimed to reconstruct the UAR from the known input signal and the related output signal based on the acoustic aspect of propagating the wave in each block. This was done to evaluate the method of estimating the UAR in the simulation and experiment.

### 2.4. FEA

FEA models engineering systems with interconnected parts [25,26]. Acoustic FEA reveals the pressure distribution in the 2D and 3D domains where the excitation source, acoustic properties and boundary conditions are defined. The aim of the FEA simulation was to model acoustic waves transmitted from the surface of the transducer and propagated through different samples and to understand refraction, reflection and scattering in the tank, which cannot be measured with a face-to-face sender-receiver transducer setup.

#### 2.4.1. Geometry

To simplify the simulation and minimize computational time and cost, a 2D geometry of each sample was created in ANSYS (ANSYS® Academic Research, Release 17.2, Help System, ANSYS, Inc.) [27] such as to determine the optimal size of the domain of the samples submerged in water. For that, the sample was placed in the centre of a circle (submerged in water) (Fig. 3). The thickness of the domain was 1/6 of the wavelength (for each frequency) in water which is similar to the size of the required elements (see below). Generally, a larger surrounding medium results in more accurate solutions as it is closer to an ideal plane wave condition (wave fronts are infinite parallel planes), as well as a larger computational domain associated with a higher computational cost. The appropriate model size can be determined by investigating a domain size dependency where the size of the water domain as the surrounding and dominant medium is systematically increased and the maximum magnitude of the sound pressure level (SPL) in the sample domain is monitored until the magnitude of maximum SPL becomes stable. This independency study was done for the two-step sample for a range of frequencies resulting in a 40 mm radius for circular domain of water.

#### 2.4.2. Elements

The 2D geometry developed above was subdivided into a number of small subdomains called elements where each element had a defined shape and number of nodes. The element size needs to be fine enough to reasonably resolve the wave propagation models. A general recommendation taken into consideration was to generate 6–20 elements per dominant wavelength along the direction of the wave [26]. In the present model, water is the dominant medium. For a 0.5–1 MHz frequency in water, the wavelength varies between 3 and 1.5 mm; therefore, the element size needs to be between 0.5 and 0.2 mm where the length of 6 elements equals the wavelength. To obtain the required size of elements and validate the FEA results, a 0.5 MHz transducer was simulated in water to estimate the near field length and compare it with the measurement and mathematical correlation.

#### 2.4.3. Boundary conditions and solver

The sparse direct solver was used to compute a finite element dynamic matrix equation:

\[
[M_F] [\ddot{\bar{f}}] + [K_F] [\bar{f}] = [\bar{f}]_0
\]  

(18)

where \([M_F]\) and \([K_F]\) are the equivalent fluid mass and stiffness matrices for the system, respectively. \([\bar{f}]_0\) is an external excitation vector in the acoustic fluid, \([\bar{f}]\) is a vector of unknown nodal acoustic pressure, and \([\ddot{\bar{f}}]\) is a vector of the second derivative of acoustic pressure with respect to time (18). The excitation source was defined as an acoustic normal surface velocity at the surface of the transducer (Fig. 3). The vibrating surface causes acoustic particles adjacent to the surface to move, generating an acoustic pressure. An acoustic contact is given as the interface between the sample and water. Of note, a fluid-solid interface was not defined between the sample and water due to the negligible displacement and deformation of the solid material, and only acoustic transduction phenomena were considered. Therefore, shear wave propagation was neglected to minimize complexity. To absorb outgoing acoustic waves from the computational domain, an acoustic radiation boundary was applied to the exterior faces of the water domain [26].

### 3. Results and discussion

#### 3.1. Study design

With an intended application of ultrasound-mediated BBB opening to treat diseases of the brain, it is required as a first step to characterize
the behavior of ultrasound waves at the attenuating skull bone. Due to the structural and mechanical complexity of the human skull, simpler 3D-printed resin samples were studied providing a precise analysis of their acoustic performance. For this purpose, experiments were conducted using 3D-printed samples with transducers operating at a range of relevant frequencies. A linear analysis was applied to interpret the data and the experiments were modeled in Simulink. The UAR and FEA analysis revealed two different types of acoustic performance as shown below. This serves as a foundation for follow-up studies using layered models (that more faithfully represent the human skull) and human skull phantoms.

### Table 3
UAR comparison at different frequencies.

<table>
<thead>
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<th>Step size of samples (mm)</th>
<th>(\lambda_{500\text{KHz}} = 4.4) mm</th>
<th>(\lambda_{1\text{MHz}} = 2.28) mm</th>
<th>(\lambda_{2.25\text{MHz}} = 1) mm</th>
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<tr>
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<td>✓</td>
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<td>(c) 12.7</td>
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<td>(d) 8.47</td>
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<td>✓</td>
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<tr>
<td>(e) 6.35</td>
<td>X</td>
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<tr>
<td>(g) 2.54</td>
<td>X</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>(h) 1.27</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Fig. 4. UAR determined experimentally for (a) a 3-step and 4-step sample at 0.5 MHz, (b) a 5- and 10-step sample at 1 MHz, and (c) a 10- and 20-step sample at 2.25 MHz.
3.2. UAR validation and results

To determine the response of the ultrasonic testbed, most importantly the effect of the cabling, which results in permanent attenuation and delay, the outer surfaces of the two coaxially aligned transducers were juxtaposed with zero space and no sample in between, and the input and output signals were recorded. Comparing the input and output signals demonstrated that the output signal had a delay of 1.32 μs with an amplitude decay of 87% due to multiple energy conversions of electrical to acoustic and vice versa.

Furthermore, acoustic properties such as speed and attenuation of water and of the 3D-printed samples were measured as shown for samples 'a' and 'b' (Fig. 1a). When there was 20 mm water between the transducers (sample 'a'), a 13.3540 μs delay and a 1509 m/s speed of sound were measured in which the permanent delay produced by the testing system was subtracted. In order to minimize the measurement error, this experiment was repeated with various distances of water occupying the space between the two transducers. For a full 3D-printed cylinder shape placed between two transducers (sample 'b' (Fig. 1b and c), the delay and speed of sound were measured as 8.87 μs and 2200 m/s, respectively. Eq. (12) was used to calculate the attenuation coefficient of samples 'a' and 'b' as listed in Table 2. These acoustic properties were applied in the simulations of all samples (Fig. 1a).

We next performed acoustic measurements and simulations followed by a comparative analysis. The general approach of applying deconvolution to the UAR is shown (Fig. 2a), the input and output data in an experiment using a 0.5 MHz transducer and sample 'd' (Fig. 2b), the simulation in Simulink using four Simulink blocks implementing four major modifications (Fig. 2c), the data obtained with the simulation for both the input and output (Fig. 2d), and finally, a comparison of the experimental and simulated data to validate our simulation efforts (Fig. 2e). Importantly, the comparison of the UAR of the experiment and simulation reveals three main peaks with a similar timing corresponding to the three separate paths (steps). This compliance between the experiment and simulation not only supports our linearity assumption and Wiener filtering method, but also verifies the simulation. Therefore, this procedure was repeated for the three frequencies (0.5, 1 and 2.25 MHz) for all samples.

Table 3 summarizes the comparison between the UAR outcome of the simulation and the experiment for each sample, revealing agreement between the simulation and experiment shown by the check mark ‘✓’ where the simulation reveals the limitation, indicated by a cross mark ‘x’. The UAR of the measurement and simulation did not match for sample 'e' (4-step sample) at 0.5 MHz, but did at 1 and 2.25 MHz (Table 3). Also, at 0.5 MHz, no match was found for samples with more than 4 steps. A non-matching behavior was observed for the 10-step sample at 1 MHz, and for the 20-step sample at 2.25 MHz. A comparison between 3- and 4-step samples at 0.5 MHz (Fig. 4a), of 5- and 10-step samples at 1 MHz (Fig. 4b), and of 10- and 20-step samples at 2.25 MHz...
is shown (Fig. 4c), revealing frequency-dependent boundary conditions. The UARs of the 4-step sample at 0.5 MHz, of the 10-step sample at 1 MHz, and of the 20-step sample at 2.25 MHz failed to determine the number of peaks according to the number of steps.

Taking physical dimensions into consideration, this threshold can be explained when the actual step size (height) and wavelength in millimeters are taken into consideration. These dimensions are a 8.47 to 6.35 mm step size with a 4.4 mm wavelength at 0.5 MHz, a 5.08 to 2.54 mm step size with a 2.28 mm wavelength at 1 MHz, and a 2.54 to 1.27 mm step size with a 1 mm wavelength at 2.25 MHz. Considering the step sizes and wavelengths, the threshold of each border can be defined as

\[ L > 1.50 \times \lambda \]  

in which \( \lambda \) is the wavelength and \( L \) is the size of the step (step height). This means that the experimental and numerical UAR of the sample can determine the separate number of steps if the step size (height) is longer than 1.50 times the wavelength in the sample. In order to investigate the linearity and negligible refraction and scattering assumption, it is necessary to use an analytical approach to examine the assumption by means of FEA of the samples immersed in water. Therefore, ANSYS was applied to characterize wave propagation through the samples.
3.3. FEA validation and results

To obtain the required size of elements and validate the FEA results, a 0.5 MHz transducer was simulated in water to estimate the near field length and compare it with the measurement and mathematical correlation. This length is a characteristic of an ultrasound transducer in which there are significant fluctuations in the sound intensity due to interference of multiple waves originating from the transducer surface. At a certain distance, the pressure waves combine to form a relatively uniform front. As illustrated (Fig. 5a), waves propagate from the surface of the transducer (vertical line on the left side) to the right side at different angles, and in a certain distance of $N$, waves combine reaching the maximum pressure. The pressure from the surface of the transducer gradually increases (Fig. 5b) and reaches its maximum at a distance of 53 mm and becomes more stable at a longer distance. The near field length can be calculated as:

$$\frac{D^2}{4n} \left(1-\frac{A}{D}\right)$$

(20)

where $N$ is the near field distance, $D$ is the diameter of the transducer, and $A$ is the wavelength at 0.5 MHz in water (0.003 m). This confirms the 53 mm near field length as predicted by the FEA result.

Next, to determine whether a 2D FEA is sufficient, we performed a 3D simulation of the 2-step sample at 0.5 MHz, followed by a measurement in the Onda tank to record the pressure map front of the sample along with the wavefront (Fig. 1d). In terms of the pressure distribution and wave directivity estimation at the front of the step, the 2D and 3D FEA data were in good agreement with the experiment revealing a linear behavior of the wave as it passes along different paths through the sample (Fig. 5c). Of note, a 3D simulation would have resulted in a massive increase of computational time and costs (600 GB memory allocated for solver) due to the high number of elements (approximately 170,000) and lower computational costs (3 GB memory allocated for solver). Therefore, 2D simulations were considered throughout this study.

Considering the frequency dependency of the UAR (Table 3), the SPL contour of each sample was determined for the three frequencies (Fig. 6). The wave propagation perpendicular to the surface of the transducer is shown for the 2- and 3-step samples, with more refraction at different angles observed for the 4-step sample. At 0.5 MHz, this results in a combination of refraction and scattering effects that increase gradually from 5 to 20 steps. A similar refraction and scattering effect can be seen for the 5- and 10-step samples at 1 MHz, and for the 10- and 20-step samples at 2.25 MHz (Fig. 6). This scattering effect is observed when the step size becomes smaller than the wavelength (see Eq. (19)). However, refraction and scattered waves are undetectable using this set-up.

Therefore, to better monitor the refraction and scattering effects and the direction of the wave propagating through each sample, polar diagrams were generated which show the directivity of the ultrasound waves (Fig. 7a and b). We found that the maximum normalized sound pressure level for the 2- and 3-step samples (black and red lines) is aligned at 0°, whereas for the 4-, 5-, 10-, and 20-step samples, the sound propagates at an angle between 10° and 30°. This is in line with the results summarized in Table 3.

4. Conclusions and outlook

The recent years have seen an increase in studies characterizing ultrasonic of skull bone and phantoms [13,28-31], including new methods to improve the ultrasound characterization of complex geometric material such as skull [32,33]. Our study experimentally and numerically investigated the acoustic performance of bone-modeling resin samples that display an increased geometrical complexity in a systematic manner, anticipating future studies in more precisely modeling the cancellous, thick skull of large animals and humans. Using two NDT transducers submerged in water, we found that the UAR and attenuation of each sample could be predicted using Wiener deconvolution. While the UAR of samples with step sizes larger than the wavelength could be accurately estimated, the prediction was not accurate when the sample had smaller step sizes. This is different from what has previously been reported [34], revealing a limitation of this approach.

We further showed that the experimental and numerical UAR of samples can be determined when the step size (height) is longer than 1.5 times of the wavelength. An FEA was performed in ANSYS to determine the importance of scattering. We found that the wave propagation (originating from the surface of the sample) is perpendicular to the surface of the transducer for 2- and 3-step samples, whereas scattering is observed at different angles already in 4-step samples, and this scattering angle gradually increases with increasing steps as shown for 0.5 MHz. Together, this reveals that the scattering of an ultrasound wave is critical for complex samples with smaller step sizes as compared to simple samples with larger step sizes. It remains to be determined how ultrasound propagates through samples that more closely model the layered structure of the human skull with two outer layers and a diploe. This will be addressed in follow-up studies, before proceeding to human skull phantoms.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.ultras.2018.05.014.

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