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Contrast-enhanced ultrasound imaging using capacitive micromachined ultrasonic transducers

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Abstract

Capacitive micromachined ultrasonic transducers (CMUTs) have a nonlinear relationship between the applied voltage and the emitted signal, which is detrimental to conventional contrast enhanced ultrasound (CEUS) techniques. Instead, a three-pulse amplitude modulation (AM) sequence has been proposed, which is not adversely affected by the emitted harmonics. In this paper, this is shown theoretically, and the performance of the sequence is verified using a 4.8 MHz linear CMUT array, and a comparable lead zirconate titanate (PZT) array, across 6 V to 60 V applied AC voltage. CEUS images of the contrast agent SonoVue flowing through a 3D printed hydrogel phantom showed an average enhancement in contrast-to-tissue ratio (CTR) between B-mode and CEUS images of 49.9 dB and 37.4 dB for the PZT array and CMUT, respectively. Furthermore, hydrophone recordings of the emitted signals showed that the nonlinear emissions from the CMUT did not significantly degrade the cancellation in the compounded AM signal, leaving an average of 2 % of the emitted power between 26 V and 60 V AC. Thus, it is demonstrated that CMUTs are capable of CEUS imaging independent of the applied excitation voltage when using a three-pulse AM sequence.

Keywords: Contrast-enhanced ultrasound imaging,
capacitive micromachined ultrasonic transducers,
amplitude modulation

1 Introduction

Recently, capacitive micromachined ultrasonic transducers (CMUTs) have become available as an alternative to the more conventional piezoelectric transducers [1, 2]. CMUTs offer sensitivity features that are particularly suitable for microbubble contrast-enhancement imaging, with low transmit pressure, yet high receive sensitivity [1]. Contrast enhanced ultrasound (CEUS) imaging with microbubble contrast agents is used clinically to study the blood's wash-in and wash-out time in organs [3], to quantify the blood-flow velocity using time-intensity curves [4], and, most recently, to image blood-flow through capillaries beyond the diffraction limit, through super-resolution ultrasound imaging (SRI) [5, 6]. CEUS imaging with a CMUT is a combination of two nonlinear processes; the spectral content of the emission from a CMUT is nonlinearly related to its excitation voltage [7], and the spectral content of the scattering of the excitation by the microbubble contrast agents is nonlinearly related to the acoustic pressure [8]. This combination poses some challenges to the conventional CEUS techniques, and the viability of CEUS imaging using CMUTs has been questioned [9].

CMUTs emit ultrasound by applying an AC voltage potential across thin plates suspended on top of nanometer to micrometer sized cavities. The technology offers great design flexibility [10], making it possible to produce transducers with several advantageous features for CEUS imaging. Firstly, the transducer can achieve wide bandwidth, resulting in high axial resolu-

tion [10]. For SRI, where separation of the microbubbles within each image frame is essential, this could enable SRI with a higher number of resolved microbubbles within each frame, and thus a lower acquisition time. The wide bandwidth would also facilitate detection of higher harmonics scattered by the microbubbles, often utilized in the pulse inversion (PI) technique. Secondly, CMUTs can produce a low emitted pressure, suitable for exciting microbubbles without destroying them [11], whilst maintaining a high receive sensitivity [12]. However, the drawback of CMUT technology is that the electrostatic force driving the excitation causes the emitted signal to contain considerable harmonic components [13]. The amount of harmonic content produced by the transducer is dependent on the ratio of the applied AC voltage to the applied DC voltage [7], which renders the transducer incapable of removing of tissue-generated signals using conventional CEUS techniques.

CEUS imaging achieves high contrast by removing the signal scattered by the tissue from that scattered by the microbubbles. The most common techniques used to remove the tissue signal are PI, amplitude modulation (AM), and singular value decomposition (SVD). The first two utilize the fact that when a bubble is insonified, it will scatter the sound nonlinearly [14]. SVD is a spatiotemporal filtering technique, which utilizes the bubble's high scattered intensity and temporally transient behavior to separate the bubbles from the tissue [5]. These techniques are thus capable of removing the linearly scattered signals caused by the tissue surrounding the contrast agents. PI combines the responses from two excitations with opposite signs [15]. Conventionally, AM is achieved by combining the response from two excitations, one with half the amplitude of the next [16]. Both the difference in amplitude and difference in polarity will cause the CMUT to emit harmonics that differ between the emissions, which

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conventional AM and PI will not be able to remove. Using such sequences with CMUTs will therefore result in poor contrast in the CEUS images [17, 18]. Several attempts have been made to overcome this issue by altering the frequency content of the emitted pulse [19, 20], but such approaches are not necessarily compatible with the bipolar pulsers often found in commercial scanners. Moreover, these methods rely on all elements in the probe behaving identically, which is often not the case. However, Fouan and Bouakaz [18] have proposed that CEUS imaging can be obtained using simple sinusoidal excitations by implementing a three-pulse AM sequence. In this sequence, the difference in amplitude between emissions, which is needed to preserve the nonlinear back-scattering from the microbubbles, is achieved by emitting once with the full active aperture, once with the odd-numbered elements, and once with the even-numbered elements. Fouan and Bouakaz [18] shows that for a single transmit voltage of 20 V applied to a CMUT, a 15 dB improvement in contrast-to-tissue ratio (CTR) was achieved, compared with an AM sequence with scaled voltage. A similar approach has been studied in [17], where it was shown that a two-pulse AM sequence with halving of the active elements resulted in better contrast than conventional PI imaging. The contrast of CEUS images is influenced by the power of the AM signal compared with the power of any remaining signal scattered by tissue, often quantified by CTR [21]. Since the applied voltage and polarity to each emitting element is constant for all emissions in these modified AM sequences, the theory predicts that the emitted signals therefore contain the same harmonics. This indicates that the increasing harmonic content resulting from increased applied AC voltage does not affect the performance of the imaging technique.

This paper investigates the two-pulse and three-pulse AM sequence at a wide range of transmit volt-

ages, corresponding to varying nonlinear components in the emissions. It is hypothesized that the amount of nonlinear harmonics in the emitted signal does not affect the efficiency of these modified AM techniques. This is demonstrated theoretically, and verified with measurements. The method's ability to cancel linear components is measured using hydrophone recordings, and its contrast enhancement is assessed using CEUS imaging of a microflow phantom with SonoVue contrast agents. The measurements are made using a linear CMUT array produced in house, and, for reference, using a corresponding commercial lead zirconate titanate (PZT) array.

2 Theory

2.1 Emission from a CMUT

The propagation of sound waves from a CMUT array is induced by applying an AC voltage, V_{AC} , across the CMUT cells. This causes a time-varying deflection, driven by electrostatic force on the cell plates. [22]. The acoustic pressure radiated from a circular cell plate is proportional to the resulting displacement of the plate [23], and the relationship between the applied voltage and the displacement is governed by a nonlinear differential equation [24]. Analytic evaluation of this equation is not straight forward, but several authors have studied the relationship numerically [22, 24, 25]. It has been shown that the emitted sound pressure from CMUTs contain harmonics to the applied excitation frequency [24, 26]. Thus, when the applied V_{AC} is a simple sinusoid at some excitation frequency, ω_0 , the resulting emitted pressure, $p(t)$, can be expressed

$$p(t) = \alpha_0 \sin(\omega_0 t) + \sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h), \quad \begin{cases} h \in \mathbb{Z}, \\ \alpha_h \in \mathbb{R}, \end{cases} \quad (1)$$

$$= p_L(t) + \sum_{h=2}^{\infty} p_H(t) \quad (2)$$

Here, t is time, α is some amplitude, h is a harmonic index, ϕ is a phase difference. Since α_h can be any real number, including zero, this notation is applicable even when only certain harmonics are present in the emitted signal. A compact form of (1) is given in (2), where $p_L(t)$ is the linear part, i.e. the component of the signal which has the same frequency content as the applied ω_0 , and $\sum p_H(t)$ is the harmonics. The amplitude and phase of the harmonics are determined by the complex dynamics of the CMUT array, and are not further described here. Notably, it has been shown that the amount of harmonic content in the emitted pressure wave depends on the ratio of the amplitude of the applied V_{AC} to the applied DC voltage [26], and CMUTs are therefore said to be inherently nonlinear. However, it will here be shown that the nature of the harmonics does not affect the effectiveness of the three-pulse AM sequence.

In the three-pulse AM sequence proposed by Fouan and Bouakaz [18], a pulse of full amplitude, p_A , is emitted, followed by two pulses of halved amplitude, p_B and p_C . The applied voltage is constant across all three emissions, and the two half amplitudes are made by halving the number of active elements compared with the full emission, spread across the same active aperture width. Thus, the three emitted pulses are

$$p_A(t) = \alpha_0 \sin(\omega_0 t) + \sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h), \quad (3)$$

$$p_B(t) = 0.5 \left[\alpha_0 \sin(\omega_0 t) + \sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right], \quad (4)$$

$$p_C(t) = 0.5 \left[\alpha_0 \sin(\omega_0 t) + \sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right]. \quad (5)$$

2.2 The amplitude modulation technique

When the microbubbles are insonified with an ultrasound pulse, the reflections contain harmonics of the incident frequency. Eckersley et al. [11] show that the nonlinear reflections can be modeled as a polynomial expansion of the incident wave, as

$$y(t) = a_1 p_i(t) + a_2 p_i^2(t) + a_3 p_i^3(t) + \dots + a_{\infty} p_i^{\infty}(t). \quad (6)$$

Here, $y(t)$ is the reflected signal, $p_i(t)$ is the incident pressure wave on the bubble, and a_i are reflection coefficients determining the different nonlinear contributions, where a_1 represents the linear reflection and $a_{i>1}$ represents the nonlinear reflections. To suppress the linear component of the emitted signal, while preserving the nonlinear components at the fundamental, the reflected signals are combined as

$$y_{AM}(t) = y_A(t) - y_B(t) - y_C(t), \quad (7)$$

where y_{AM} is the remaining three-pulse amplitude modulation signal, and y_A, y_B, y_C are the scattered signals caused by the three emissions. If instead, only 2 emissions are used the combination is made as

$$y_{AM}(t) = y_A(t) - 2 \cdot y_B(t). \quad (8)$$

2.3 Amplitude modulation with a CMUT

By assuming that no distortion of the signal occurs between the emission and the bubble position, we can apply (6) to the three emissions given in (3) - (5) before applying (7). By expressing the pressure waves in their compact form and limiting the polynomial expansion

¹to third order for simplicity, this gives

$$\begin{aligned} y_{AM}(t) = & a_1 p_A + a_2 p_A^2 + a_3 p_A^3 - a_1 p_B - a_2 p_B^2 \\ & - a_3 p_B^3 - a_1 p_C - a_2 p_C^2 - a_3 p_C^3. \end{aligned} \quad (9)$$

⁵Then, by expanding to the long form of (3) - (5), setting $\alpha_0 = 1$, working through the algebra (shown in more detail in the appendix) gives

$$\begin{aligned} y_{AM}(t) = & 0.5 a_2 \sin(\omega_0 t)^2 \\ & + 0.5 a_2 \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right)^2 \\ & + a_2 \sin(\omega_0 t) \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right) \\ & + 2.25 a_3 \sin(\omega_0 t) \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right)^2 \\ & + 2.25 a_3 \sin(\omega_0 t)^2 \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right) \\ & + 0.75 a_3 \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right)^3 \\ & - 0.1875 a_3 \sin(3\omega_0 t) \\ & + 1.5 a_3 \sin(\omega_0 t). \end{aligned} \quad (10)$$

²⁴Two important observations can be made about (10).
²⁵Firstly, it reveals a subtle, but, essential property of
²⁶AM imaging; the remaining signal lacks any linearly
²⁷scattered components, yet, the last term of (10) contains
²⁸energy at the fundamental frequency. The reflection
²⁹coefficient a_3 indicates that this component
³⁰is caused by the nonlinear scattering properties of the
³¹microbubbles. Secondly, it is observed that this cancellation
³²of the linearly scattered signal was attained
³³despite the nonlinear nature of the CMUT. Although
³⁴harmonics to the fundamental frequency are emitted,
³⁵as seen in (3) - (5), (10) does not contain any emitted
³⁶harmonics with the linear reflection coefficient a_1 .
³⁷This shows that when the emitted signals are reflected
³⁸only linearly, the AM compounding cancels all of these
³⁹terms. Some emitted harmonics remain in the y_{AM} sig-

nal, but, these terms all carry the reflection coefficients¹
 a_2 or a_3 , meaning that the signals have been nonlinearly²
scattered by the microbubble. Notably, the fact³
that these emitted harmonics remain in the y_{AM} signal⁴
has not impaired the efficiency of the AM theory.⁵
Moreover, although the amplitude and phase of the⁶
emitted harmonics will be affected by the amplitude⁷
of V_{AC} , this does not affect the cancellation of linearly⁸
scattered signals. Because of this, when using the AM⁹
modality to image *in vivo* with a CMUT, it is possible¹⁰
to filter out linear scattering from tissue whilst attaining¹¹
reflections from the microbubbles at the emitted¹²
frequency. Thus, it is shown theoretically that CEUS¹³
imaging with a CMUT using the three-pulse AM sequence¹⁴
is achievable.

3 Methods

To verify the outcome of the theoretical evaluation¹⁸
shown in Section 2, the ability of a linear CMUT array¹⁹
to cancel received linear components while preserving²⁰
nonlinearly scattered signal was assessed using three²¹
measurement set-ups. Firstly, an experimental set-up²²
was designed to quantify CTR. Section 3.1 outlines²³
the design of the set-up. Contrast enhanced AM images²⁴
were collected using a synthetic aperture imaging²⁵
sequence on a CMUT and a PZT probe, further²⁶
described in Section 3.2. Subsequently, the CTR was²⁷
calculated for all the collected images, as detailed in²⁸
Section 3.3. Secondly, Section 3.4 describes how the²⁹
emitted signal from the transducers were recorded using³⁰
a hydrophone, and used to determine the peak-negative-³¹
pressure (PNP) and the power annihilation³²
ratio. Lastly, Section 3.5 describes how the signal-to-³³
noise ratio of the two probes were evaluated to fairly³⁴
compare the CMUT's and PZT arrays's performance.

3.1 CEUS imaging set-up

The experimental set-up used to quantify CTR consisted³⁸
of a microflow phantom and a block of tissue-

Figure 1: An illustration of the experimental set-up showing how the phantom and tissue-mimicking material are positioned under the transducer and held in place by a brace. The transducer sits directly above the phantom and tissue-mimicking material, in contact with the water.

Table 1: Specifications of the transducers.

	CMUT	PZT
Total number of elements	192	192
Center frequency	4.8 MHz	5.2 MHz
Pitch (p)	0.2 mm	0.2 mm
Kerf	0.02 mm	0.02 mm
Maximum tolerable AC voltage	60 V	100 V
Applied DC voltage	190 V	N/A

3.2 Image acquisition

The phantom and tissue-mimicking material was imaged using a linear CMUT [30] and, as a reference, a commercial linear PZT array of equivalent dimensions, using a Verasonics research scanner (Verasonics Vantage 256). The specifications of the probes are given in Table 1. The set-up was imaged using a synthetic aperture sequence [31] with low intensity diverging wave propagation. A summary of the sequence parameters are given in Table 2. The transducers emitted a 2 cycle sine wave at 4.8 MHz, with 32 active elements in each full amplitude emission, and with a pulse repetition frequency of 1000 Hz. The sequence

Figure 2: An illustration of the phantom, where the bold black line illustrates the internal channel.

mimicking material. An illustration of the measurement set-up can be seen in Fig. 1. The microflow phantom was 3D printed in a PEGDA 700 g mol⁻¹ hydrogel block using stereo-lithography. A hollow channel of 200 μ m in diameter was printed inside the phantom, as shown in Fig. 2. The fabrication process of the phantom has been described in [27]. The phantom was held in place by a brace next to a block of tissue-mimicking material made of polyvinyl alcohol cryogel [28, 29], resulting in scattering properties similar to that of human tissue. The ensemble was placed in a water bath, which was lined with an acoustic absorber. The phantom was positioned so that the center of the flow channel was 25 mm below the surface of the transducer. A low pressure flow pump (neMESYS 290N, Cetoni) fitted with a syringe of SonoVue microbubble contrast agents, diluted 1:10 with saline, was connected to the phantom and used to pump microbubbles through the phantom.

¹Table 2: Parameters of the synthetic aperture se-
²quence.

³	Pulse repetition frequency	1000 Hz
⁴	Number of active elements	32
⁵	Emission frequency	4.8 MHz
⁶	Focal distance	-16 mm
⁷	Receive F-number	1
⁸	Number of emissions (n)	13
⁹	Number of cycles in emission	2
¹⁰	Number of elements separating emissions (s)	13

¹³consisted of emissions from $n = 13$ virtual sources
¹⁴placed 16 mm behind the transducer surface. The lat-
¹⁵eral positions of the virtual sources were given by

$$¹⁷ $x_i = s \cdot i \cdot p, \forall i \in \mathbb{Z} : i \in [-\frac{(n-1)}{2}, \frac{(n-1)}{2}]$,
¹⁸ (11)
¹⁹$$

²⁰where s denotes the number of elements separating
²¹the lateral positions of two virtual sources, i is emis-
²²sion index, p is the transducer pitch, and $x_i = 0$ lays
²³in the middle of the transducer. The three emissions
²⁴described in (3) - (5) are referred to as the minor se-
²⁵quence. The minor sequence was emitted once by each
²⁶virtual source at each x_i to make a full image frame.

²⁷ The sequence was used to quantify how the CTR in
²⁸the resulting images vary with the applied AC voltage.
²⁹The lowest V_{AC} was 6 V, at which the imaging system
³⁰approaches its noise floor. For the CMUT, V_{AC} was
³¹then increased in steps of 10 V until the maximum tol-
³²erable AC voltage of the probe, as given in Table 1,
³³was reached. Additionally, a constant DC voltage of
³⁴190 V was applied to the CMUT, as specified in [30].
³⁵For the PZT array, the same voltage range was used,
³⁶from 6 V to the probe's maximum tolerable voltage.
³⁷But, the step size was reduced to 3 V between 6 V and
³⁸15 V. This was done to ensure a good population of
³⁹data-points within the overlapping range of PNP for

the two probes, since the relationship between applied¹
voltage and PNP is not linear.²

³ The SonoVue solution was allowed to flow contin-
⁴uously through the phantom channel at $0.6 \mu\text{L s}^{-1}$,
⁵while 10 image frames were collected at each V_{AC} . To
⁶avoid degradation of the microbubbles during the col-
⁷lection of the 10 frames, a pause of 15 s was inserted
⁸between each frame to allow a fresh batch of microbub-
⁹bles to flow into the phantom. A fresh syringe of di-
¹⁰luted contrast agents were prepared directly prior to
¹¹each data-set acquisition. Due to the higher number of
¹²AC voltages, the acquisition using the PZT probe was
¹³divided into two data-sets to make the time each sy-
¹⁴ringe spent in the infusion pump comparable for each
¹⁵data-set. Thus, 3 data-sets were acquired; 6 V to 60 V
¹⁶with the CMUT, and 6 V to 26 V as well as 26 V to
¹⁷90 V with the PZT array.
¹⁸

²⁰3.3 Calculation of CTR

²¹ The collected data from both probes were matched
²²filtered and beamformed using delay-and-sum beam-
²³forming. CEUS images were composed using both (7)
²⁴and (8). The two-pulse AM sequence, which was also
²⁵studied by the authors in [32], is included for compar-
²⁶ison with the three-pulse AM proposed by Fouan and
²⁷Bouakaz [18], to study how an additional emission in
²⁸the minor sequence affects the image quality. In ad-
²⁹dition, the data from every full amplitude emission in
³⁰the minor sequence was used to compose B-mode im-
³¹ages, for comparison. For each composed image, the
³²CTR was calculated as
³³

$$³⁴ $CTR = \frac{P_B}{P_{TMM}}$,
³⁵ (12)
³⁶$$

³⁷where P_B is the average power of the signal scattered
³⁸by the bubbles and P_{TMM} is the average power scat-
³⁹tered by the tissue-mimicking material. The average

power was calculated as

$$P = \frac{1}{L_2 - L_1} \frac{1}{k_2 - k_1} \sum_{l=L_1}^{L_2} \sum_{m=k_1}^{k_2} y_{l,m}^2, \quad (13)$$

where y is the signal in a single beamformed line of data, m is the sample number, k_1 and k_2 are sample numbers determining the axial position for the signal, and L_1 and L_2 are line numbers. Thus, the power was calculated in two rectangular regions-of-interest (ROIs). After beamforming the collected data, the ROIs used to calculate power in (13) were drawn around the channel in the phantom. The ROI in the tissue-mimicking phantom was taken to be the same size as the channel ROI, and placed at the same depth, in the middle of the tissue-mimicking phantom.

17

3.4 Hydrophone recordings

The derivation of (10) assumes that the same signal is produced by the full emission as the two half emissions combined. Array effects could arguably make the assumption fail if emission from one CMUT cell affects the emission from a neighbouring cell. It has been shown that the emission from an array of CMUTs is dependent on the distance between adjacent cells [25]. This distance varies between the emissions in the proposed sequences; in the full amplitude emissions the distance is one pitch, while in the half amplitude emissions it is $2 \cdot \text{pitch}$. To evaluate if this effect adversely affects the similarity of the emitted pulses, and thus the cancellation of received linear terms, the signals emitted by each virtual source were recorded using a hydrophone. The hydrophone was placed in a water tank directly beneath the transducer, at $(y, z) = (0, 25)$ mm and moved to the x -positions corresponding to each virtual source, given by (11). The hydrophone recorded the minor sequence using all the applied AC voltages, from each virtual source. Then, the sequence's ability to cancel linear terms was

quantified by defining an annihilated power ratio as

$$\text{Annihilated power ratio} = \frac{\Sigma p_A^2 - \Sigma p_{AM}^2}{\Sigma p_A^2}. \quad (14)$$

Here, the numerator contains the remaining AM signal subtracted from the full emitted signal and thus gives the power of the annihilated signal. For each x -position and applied V_{AC} , the recordings of the minor sequence were used to compose the compounded emitted AM signal, p_{AM} , according to (7), and the annihilated power ratio. This evaluation will be affected by nonlinear propagation in the water. The evaluation was therefore performed using both the PZT array and CMUT for comparison, to distinguish effects caused by nonlinear propagation from the effects caused by nonlinear excitation.

In addition, the measured hydrophone signals were used to quantify the PNP caused by each applied V_{AC} for both transducers. The minimum of the recording of the full emission was found from the recording beneath each virtual source and averaged to give the PNP.

3.5 Quantifying signal-to-noise ratio

Because the imaging performance of a CMUT and a PZT transducer are to be compared, it is prevalent to also quantify and compare the signal-to-noise ratio (SNR) of the two transducers. The three-pulse AM imaging sequence was used to acquire $N = 10$ frames of a speckle phantom with $0.5 \text{ dB cm}^{-1} \text{ MHz}^{-1}$ attenuation. Only the full emission was used to beamform B-mode images of the phantom, using the same axial sampling and depths as the images acquired of the microflow phantom in Section 3.2. The acquisition was repeated using both the PZT transducer and the CMUT for the range of applied AC voltages specified in Section 3.2, with a step-size of 10 V. After beamforming, the power of an image line located at $x = 0$ was extracted from the images, and the SNR was quantified

$$\text{SNR} = \frac{1}{N} \sum_{N=1}^{10} \frac{\sum_{m=k_1}^{k_2} \bar{y}^2}{\sum_{m=k_1}^{k_2} (y - \bar{y})^2}, \quad (15)$$

where y is the image line and $\bar{y}$ represents the average of the image line across the 10 acquisitions.

4 Results

Fig. 3 shows examples of a B-mode image and both a two-pulse and a three-pulse AM image of the microflow phantom and tissue-mimicking material, where the chosen ROIs are drawn on top of the images. In the images, it is clear that both the AM sequences with both probes have succeeded in removing most of the speckle pattern from the tissue-mimicking phantom, whereas the signal from the microbubbles remains. More speckle pattern remains in the AM images composed with two pulses, indicating that the three-pulse sequence outperforms the two-pulse sequence. The similarity of the images collected with the CMUT, in the left column of Fig. 3, and the PZT transducer, in the right column, gives a clear indication that CEUS with a CMUT is possible, despite the nonlinear nature of the probe.

Equations (12) and (13) were applied to all the collected images, both in three-pulse AM, two-pulse AM, and B-mode to calculate their CTR. The mean and standard deviation of the CTR was calculated for each set of 10 frames collected with constant V_{AC} . Fig. 4 shows the resulting mean CTR values with standard deviations as a function of V_{AC} applied to the CMUT for the three-pulse AM and B-mode, in addition to the difference between the two in decibels. Comparing the two modes shows that the CMUT has achieved a significant contrast enhancement across all the applied AC voltages, with 30 - 38 dB higher CTR in the CEUS images than in the B-mode.

Although the theory of the three-pulse AM sequence, presented in Section 2, predicts that CTR should not

degrade as the amount nonlinearity in the emitted signal rises with the applied AC voltage, it is expected that the CTR varies with AC voltage due to the nature of the microbubble contrast agents. As the applied voltage increases, so does the PNP of the emitted signal, which affects both the power and the spectral content of the scattered signal from the microbubbles [33]. Therefore, to fully understand the observed variation in CTR seen in Fig. 4, in Fig. 5, the CTR values are also plotted as a function of the emitted PNP, as recorded by the hydrophone measurements. In addition, the CTR of the B-mode and CEUS images collected using the PZT probe are plotted, to provide a reference of how the CTR varies with PNP when the emission from the probe is linear. The CTR for the PZT array is divided into two data-sets, representing the images collected with separate syringes of SonoVue.

The compounded AM signals were computed from the collected hydrophone recordings, using (7), and the annihilated power ratio was calculated as in (14). Fig. 6 shows how the power ratio varies with PNP. Had the cancellation of the signals been completely successful, all power would be removed and the power ratio would be 100 %. That is not the case, and it can be seen that the power ratio declines as PNP increases above approximately 455 kPa. In the region where the two probes' PNP overlap, the power ratios of both the PZT transducer and the CMUT are high, indicating that the emitted signals are suitable for CEUS imaging, and that the efficiency of the three-pulse sequence is not affected by the increase in nonlinearity in the emitted signal from the CMUT, as the AC voltage is increased.

Finally, the SNR of the image acquisition using the two probes at varying AC voltages were calculated according to (15). The measured SNR is given in Table 3. Generally, it is seen that the SNR of the CMUT probe

Figure 3: Example images of the experimental set-up collected with the CMUT probe (left column) and PZT transducer (right column). Comparing the B-mode (a and b) with the two-pulse AM images (c and d) and the three-pulse AM image (e and f) show that the three-pulse sequence has successfully removed the speckle pattern inside the tissue-mimicking material (on the right of the image), while retaining the signal from the microbubbles (on the left of the image). The magenta and cyan boxes show the regions of interest used to calculate the CTR.

is lower than the PZT transducer, with a mean difference of 16 dB across 6 V to 56 V applied AC voltage. Further discussion of the data will be given in Section 5.

5 Discussion

As predicted by the theory laid out in Section 2, Fig. 4 shows that the CTR of the CEUS images collected with the CMUT using the three-pulse AM se-

quence is not affected by the increase in nonlinear emission caused by an increasing AC voltage. There is a significant enhancement of contrast between the CEUS images and the B-mode images, with an average of 35.3 dB enhancement across the applied voltages. Moreover, although the CTR of the CEUS images shown in Fig. 4 declines above 46 V, the difference between the logarithm of the CTR of the CEUS images and the B-mode images increases from 26 V to 60 V,

¹Table 3: The measured SNR of the CMUT and PZT arrays across all of the applied AC voltages. The SNR is ¹
²calculated according to (15) and displayed with $\pm$ one standard deviation, σ . ²

AC voltage (V)	6	16	26	36	46	56	60	66	76	86	90
CMUT SNR $\pm \sigma$ (dB)	37 $\pm$ 4	50 $\pm$ 6	61 $\pm$ 7	65 $\pm$ 6	71 $\pm$ 6	72 $\pm$ 6	72 $\pm$ 6	N/A	N/A	N/A	N/A
PZT SNR $\pm \sigma$ (dB)	71 $\pm$ 5	64 $\pm$ 4	75 $\pm$ 5	80 $\pm$ 6	81 $\pm$ 7	84 $\pm$ 5	N/A	87 $\pm$ 5	92 $\pm$ 5	92 $\pm$ 5	85 $\pm$ 5

¹⁷Figure 4: The calculated CTR values of the images ¹⁷
¹⁸collected with the CMUT using the three-pulse AM ¹⁸
¹⁹sequence, as a function of the applied AC voltage. ¹⁹
²⁰The shaded areas indicated $\pm$ one standard deviation, ²⁰
²¹calculated from the repeated acquisitions at each ²¹
²²applied AC voltage. The green lines give the ²²
²³CTR of the CEUS and B-mode images, while the ²³
²⁴blue line gives the difference between the two. ²⁴

²⁸demonstrating that the enhancement of the contrast ²⁸
²⁹caused by the three-pulse AM sequence is not affected ²⁹
³⁰by the applied AC voltage. On the other hand, it can ³⁰
³¹be seen in Fig. 5 that the two-pulse AM sequence has ³¹
³²not accomplished the same enhancement. Clearly, re- ³²
³³ducing the number of emissions in the minor sequence, ³³
³⁴would benefit the frame rate. However, the average dif- ³⁴
³⁵ference in CTR between the CEUS images and the B- ³⁵
³⁶mode images for the two-pulse AM sequence is only ³⁶
³⁷9.1 dB. Thus, CEUS imaging using a CMUT should ³⁷
³⁸use the three-pulse AM sequence, despite the decrease ³⁸
³⁹in frame rate this will lead to. ³⁹

¹⁷Figure 5: The calculated CTR values of the images ¹⁷
¹⁸collected with the CMUT and PZT transducer, as a ¹⁸
¹⁹function of the emitted peak-negative-pressure. The ¹⁹
²⁰CTR of three-pulse AM images are plotted with ²⁰
²¹solid lines, of the two-pulse AM images with solid ²¹
²²lines with diamonds, and the CTR of the B-mode ²²
²³images are plotted with dotted lines. The shaded ar- ²³
²⁴reas indicated $\pm$ one standard deviation, calculated ²⁴
²⁵from the repeated acquisitions at each applied AC ²⁵
²⁶voltage. ²⁶

²⁸The CTR of the CEUS images follows the expected ²⁸
²⁹trend; it increases initially, before starting to de- ²⁹
³⁰crease at higher voltages. This progression is caused ³⁰
³¹by the back-scattering properties of microbubbles. At ³¹
³²low pressures, the nonlinear component of the back- ³²
³³scattering from microbubbles is proportional to the in- ³³
³⁴cident acoustic pressure [33, 34], and Emmer et al. [35] ³⁴
³⁵showed that SonoVue exhibits a low pressure thresh- ³⁵
³⁶old, under which the bubbles do not scatter nonlin- ³⁶
³⁷early. On the other hand, at high pressures, the CTR ³⁷
³⁸is expected to drop because the microbubbles start ³⁸
³⁹

Figure 6: The average percentage ratio of power annihilated in the AM signal, normalized to the emitted power. A power ratio of 100 % indicates that all of the power in the AM signal was removed. Error bars indicate $\pm$ one standard deviation of variation along virtual source (VS) positions.

ducer as for the images collected using the CMUT,¹ further reinforcing that the decline is not caused by² a deterioration of the three-pulse AM sequence. The³ PZT transducer displays a rapid decline in CTR above⁴ 455 kPa, likely caused by both the microbubble disrupt-⁵ tion discussed above, but also by nonlinear propaga-⁶ tion in the image medium. The ratio of annihilated⁷ power shown in Fig. 6 also declines above 455 kPa,⁸ pointing to a discrepancy in the emitted pulses. Obser-⁹ vation of the recorded hydrophone signals reveal saw-¹⁰ tooth like pulse shapes, indicative of nonlinear propa-¹¹ gation [39]. This distortion of the emitted pulses will¹² differ between the full amplitude and half amplitude¹³ emissions, and thus cause the cancellation in (7) to¹⁴ fail.¹⁵

Although the same AC voltage was applied to the¹⁸ CMUT and the PZT transducer, up to the maximum¹⁹ tolerable AC voltage of the CMUT, the PZT trans-²⁰ ducer emits higher PNP than the CMUT. The two²¹ probes have some overlap in their area of operation be-²² tween 101 kPa to 258 kPa. In this region, both probes²³ exhibit a significant contrast enhancement, with an av-²⁴ erage difference in CTR between the CEUS images and²⁵ the B-mode images of 49.9 dB and 37.4 dB for the PZT²⁶ transducer and CMUT, respectively. The fact that the²⁷ PZT transducer overall performs better contrast en-²⁸ hancement than the CMUT is likely caused by the²⁹ PZT transducer's superior SNR. At a constant emit-³⁰ ted pressure, the back-scattering from the microbub-³¹ bles will generally be the same for the PZT transducer³² and CMUT. Yet, the CTR can differ, if the amount of³³ received noise is higher for the CMUT. As shown in Ta-³⁴ ble 3 the CMUT has a lower SNR than the PZT trans-³⁵ ducer at all applied voltages. This is expected, since³⁶ the probe is built in-house, whereas the PZT trans-³⁷ ducer is a commercial probe and has superior shielding³⁸ from electromagnetic interference noise.³⁹

to degrade, through processes such as rupture of the¹⁹ lipid shell, diffusion of the gas core, or fragmentation²⁰ [36–38]. A decline in CTR of the CEUS images col-²¹ lected with the CMUT is observed in Fig. 4 starting²² at 46 V, and correspondingly in Fig. 5 at 203 kPa. How-²³ ever, this decline in CTR does not point to a failure²⁴ of the three-pulse AM sequence, but rather a natu-²⁵ ral consequence of the properties of the microbubbles.²⁶ According to de Jong et al. [33], SonoVue can with-²⁷ stand up to 150 kPa before it starts to deform, and it²⁸ is destroyed with a few repeated ultrasound exposures²⁹ above approximately 300 kPa. This corresponds to the³⁰ range at which the CTR in Fig. 5 starts to decline, tak-³¹ ing into account the attenuation the emitted signal will³² experience before reaching the microbubbles inside the³³ phantom. Thus, it has been shown that the ideal pres-³⁴ sure range to perform CEUS imaging with a CMUT³⁵ lies approximately between 100 kPa to 200 kPa.³⁶

Moreover, the same downwards trend in CTR of³⁷ the CEUS images above approximately 100 kPa is ob-³⁸ served for the images collected using the PZT trans-³⁹

¹ Yet, the quantification of the annihilated power
²shown in Fig. 6 shows that the CMUT generally out-
³performs the PZT transducer. The power annihilation
⁴ratio quantifies how much power that remains in the
⁵compounded emission and thus gives an indication of
⁶how well the transducers are able to perform contrast
⁷enhancement imaging. The cancellation of the emit-
⁸ted pulses is more effective for the CMUT than the
⁹PZT transducer, indicating that array effects in the
¹⁰CMUT is not causing significant degradation of the
¹¹contrast enhancement. In the region where the two
¹²probes' PNPs overlap, the compounding of the AM
¹³signal from the CMUT leaves an average of 2 % of the
¹⁴emitted power, while for the PZT transducer the av-
¹⁵erage remaining power is 7 %. When using the emis-
¹⁶sions for imaging, the amount of remaining power will
¹⁷transfer to the scattered signals and impair the ability
¹⁸to cancel linear signal from the tissue, thus lowering
¹⁹the CTR. Moreover, both probes exhibit an increase
²⁰in the annihilated power with applied AC voltage, as
²¹well as an increased standard deviation of the annihi-
²²lated power at low applied AC voltages. This further
²³supports that the nonlinear emission from the CMUT
²⁴does not negatively impact the creation of CEUS im-
²⁵ages using the proposed three-pulse AM sequence.

²⁷6 Conclusion

²⁸Investigation of the creation of CEUS images with a
²⁹CMUT has shown that the probe's inherent nonlin-
³⁰earity does not affect its performance, and that high
³¹contrast CEUS images can be created using a three-
³²pulse AM sequence. The fact that the performance of
³³the CMUT probe is not dependent on the harmon-
³⁴ics of its emissions has been demonstrated theoret-
³⁵ically, using quantification of CTR of CEUS images of
³⁶microbubbles, and using hydrophone measurements of
³⁷the emitted signals. Theoretically, it has been shown
³⁸that there is no reason why the emitted harmonics will
³⁹affect the CEUS images. This was confirmed by the ac-

quired CEUS images, where an average of 37.4 dB con-
trast enhancement was achieved, using the three-pulse
AM sequence. Comparison of the CTR of the images
obtained using the proposed three-pulse AM sequence
with the CTR of images obtained using only 2 emis-
sions showed a significant advantage of the three-pulse
AM, as the two-pulse AM sequence gave only an aver-
age of 9.07 dB contrast enhancement. Thus, a higher
number of emissions in the minor sequence must be
used, despite its negative impact on the frame rate.
Further, comparison of the performance of the CMUT
with a PZT transducer of similar design showed a com-
parable amount of contrast enhancement, as the im-
ages produced with the PZT transducer achieved an
average of 49.9 dB contrast enhancement. The PZT
transducer achieved higher CTR, but also higher SNR,
and improvement of the design of the CMUT, espe-
cially focused on noise shielding, will likely improve
its contrast enhancement abilities. Finally, hydrophone
recordings and quantification of the annihilated power
in the minor sequence showed that in the region of
overlapping PNPs, the CMUT annihilated 98 % of the
power, whereas the PZT transducer only annihilated
93 %. Thus, more power was cancelled in the CMUT's
minor sequence than in the PZT transducer's, fur-
ther reinforcing that the difference between the CTR
produced by the CMUT and the PZT transducer is
caused by the probes respective receive capabilities,
rather than the emitted harmonics. Thus, future use
of CMUT technology for CEUS images show great po-
tential, and it will be possible to take advantage of the
wide bandwidth, low emission pressure, and favorable
sensitivity features of CMUTs for CEUS imaging.

³⁵7 Declarations

³⁶7.1 Abbreviations

³⁷**AM** Amplitude modulation.

³⁸**CEUS** Contrast enhanced ultrasound.

³⁹**CMUT** Capacitive micromachined ultrasonic transducer.

CTR Contrast-to-tissue ratio.

¹**PI** Pulse inversion.

²**PNP** Peak-negative-pressure.

³**PZT** Lead zirconate titanate.

ROI Region-of-interest.

⁴**SNR** Signal-to-noise ratio.

⁵**SRI** Super-resolution ultrasound imaging.

⁶**SVD** singular value decomposition.

VS Virtual source.

⁸7.2 Ethics approval and consent to participate

⁹Not applicable.

¹⁰7.3 Consent for publication

¹¹Not applicable.

¹²7.4 Availability of data and material

¹³The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

¹⁴

¹⁵7.5 Competing interests

¹⁶The authors declare that they have no competing interests.

¹⁷7.6 Funding

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²⁰

²¹7.7 Authors' contributions

²²S.H. Øygard wrote the main manuscript text and prepared the figures. M.

²³L. Ommen manufactured the phantom and designed part of the

²⁴experimental set-up. B. G. Tomov assisted with technical measurements. S.

²⁵E. Diederichsen manufactured the CMUT probe. E. V. Thomsen, N. B.

²⁶Larsen, M. B. Stuart, and J. A. Jensen contributed to designing the study and discussed the results. All authors reviewed the manuscript.

²⁷

²⁸7.8 Acknowledgments

²⁹Not applicable.

³⁰**8 Appendix**

³¹The tree emissions given in (3) - (5) can be written on the compact form seen in (2) as

$$p_A(t) = p_L + \sum_{h=2}^{\infty} p_H, \quad (16)$$

$$p_B(t) = 0.5 p_L + 0.5 \sum_{h=2}^{\infty} p_H, \quad (17)$$

$$p_C(t) = 0.5 p_L + 0.5 \sum_{h=2}^{\infty} p_H. \quad (18)$$

³⁶The emissions in this form are inserted into (9);

$$\begin{aligned} y_{AM}(t) = & a_1 p_A + a_2 p_A^2 + a_3 p_A^3 \\ & - a_1 p_B - a_2 p_B^2 - a_3 p_B^3 \\ & - a_1 p_C - a_2 p_C^2 - a_3 p_C^3 \end{aligned} \quad (19)$$

$$\begin{aligned} = & a_1 \left(p_L + \sum_{h=2}^{\infty} p_H \right) + a_2 \left(p_L + \sum_{h=2}^{\infty} p_H \right)^2 \\ & + a_3 \left(p_L + \sum_{h=2}^{\infty} p_H \right)^3 - a_1 \left(0.5 p_L + 0.5 \sum_{h=2}^{\infty} p_H \right) \\ & - a_2 \left(0.5 p_L + 0.5 \sum_{h=2}^{\infty} p_H \right)^2 - a_3 \left(p_L + \sum_{h=2}^{\infty} p_H \right)^3 \\ & - a_1 \left(0.5 p_L + 0.5 \sum_{h=2}^{\infty} p_H \right) \\ & - a_2 \left(0.5 p_L + 0.5 \sum_{h=2}^{\infty} p_H \right)^2 - a_3 \left(p_L + \sum_{h=2}^{\infty} p_H \right)^3. \end{aligned} \quad (20)$$

Canceling terms and expanding the parenthesis gives

$$\begin{aligned} y_{AM}(t) = & 0.5 a_2 p_L^2 + 0.5 a_2 \left(\sum_{h=2}^{\infty} p_H \right)^2 \\ & + a_2 p_L \left(\sum_{h=2}^{\infty} p_H \right) + 2.25 a_3 p_L \left(\sum_{h=2}^{\infty} p_H \right)^2 \\ & + 2.25 a_3 p_L^2 \left(\sum_{h=2}^{\infty} p_H \right) \\ & + 0.75 a_3 \left(\sum_{h=2}^{\infty} p_H \right)^3 + 0.75 a_3 p_L^3. \end{aligned} \quad (21)$$

The long form of (3) - (5) are then reintroduced;

$$\begin{aligned} y_{AM}(t) = & 0.5 a_2 \sin(\omega_0 t)^2 \\ & + 0.5 a_2 \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right)^2 \\ & + a_2 \sin(\omega_0 t) \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right) \\ & + 2.25 a_3 \sin(\omega_0 t) \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right)^2 \\ & + 2.25 a_3 \sin(\omega_0 t)^2 \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right) \\ & + 0.75 a_3 \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right)^3 \\ & + 0.75 a_3 \sin(\omega_0 t)^3. \end{aligned} \quad (22)$$

Finally, the last term of (22) is expanded to give

$$\begin{aligned} y_{AM}(t) = & 0.5 a_2 \sin(\omega_0 t)^2 \\ & + 0.5 a_2 \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right)^2 \\ & + a_2 \sin(\omega_0 t) \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right) \\ & + 2.25 a_3 \sin(\omega_0 t) \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right)^2 \\ & + 2.25 a_3 \sin(\omega_0 t)^2 \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right) \\ & + 0.75 a_3 \left(\sum_{h=2}^{\infty} \alpha_h \sin(h\omega_0 t + \phi_h) \right)^3 \\ & - 0.1875 a_3 \sin(3\omega_0 t) + 1.5 a_3 \sin(\omega_0 t). \end{aligned} \quad (23)$$

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