Evaluation of CMUT for passive monitoring of microbubble-assisted ultrasound therapies

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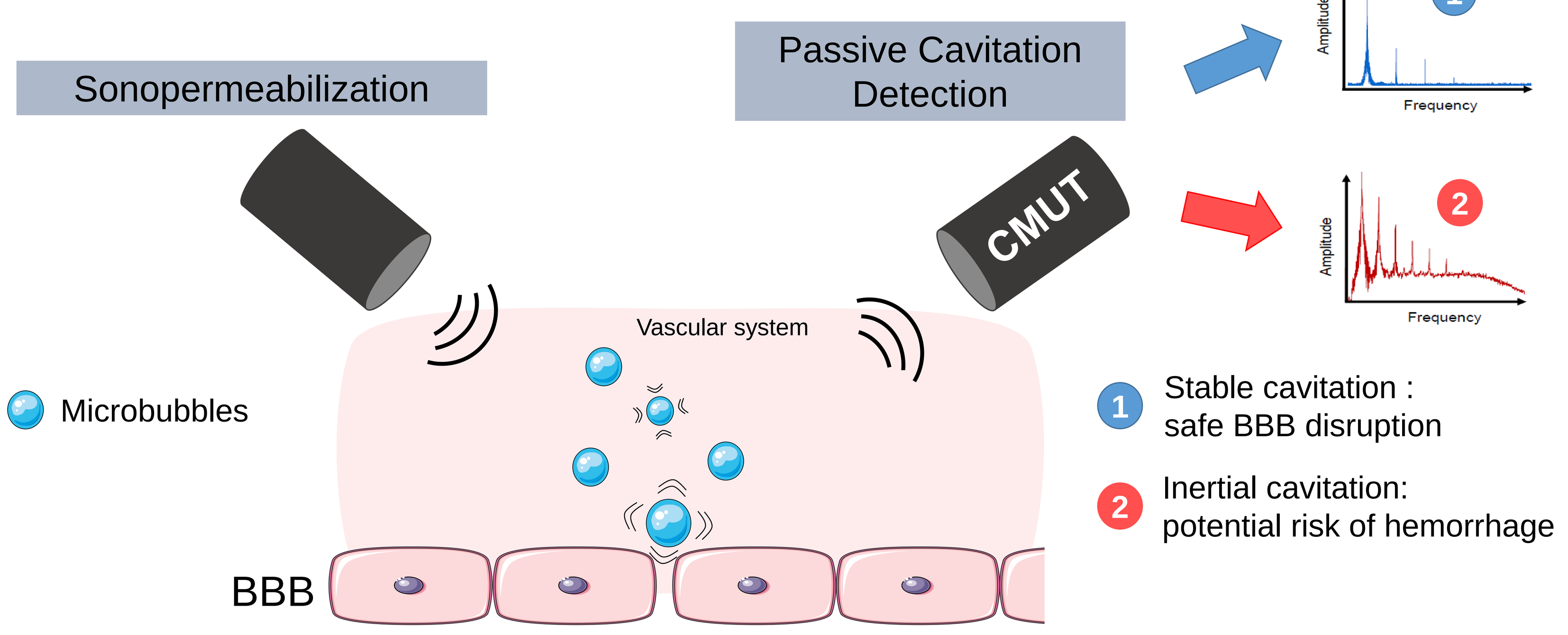
BACKGROUND / MOTIVATION

Upon suitable excitation produced by ultrasound (US), **microbubbles (MB)** can permeabilize biological barriers such as the blood-brain barrier (BBB).

→ A fine control of US parameters is crucial to avoid vascular damage due to excessive MB activity.

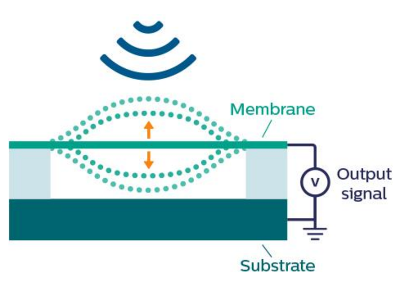


MB nonlinear response, in particular **ultraharmonics (UH)**[1], can be monitor with **passive cavitation detection (PCD)** to prevent brain damages.

Here, we propose to overcome the restricted bandwidth of piezoelectric (PZT) transducers by exploiting the unique properties of a **CMUT**, used in receive mode only, to ensure the safety of the US protocol through **wideband PCD.**

METHODS

1) 3 CMUT (square shaped, 8x8 mm^2, 400 nm gap) single-elements were developed for comparison with a standard PZT (V306-SU Olympus, Tokyo, Japan) centered at 2.25MHz used as gold standard:



Principle of a CMUT cell
(*source : philips.com*)

CMUT-based PCD (37x37 µm²)

Dimension	Active surface area
37×37µm²	50 %
32×32µm²	40 %
27×27µm²	35 %

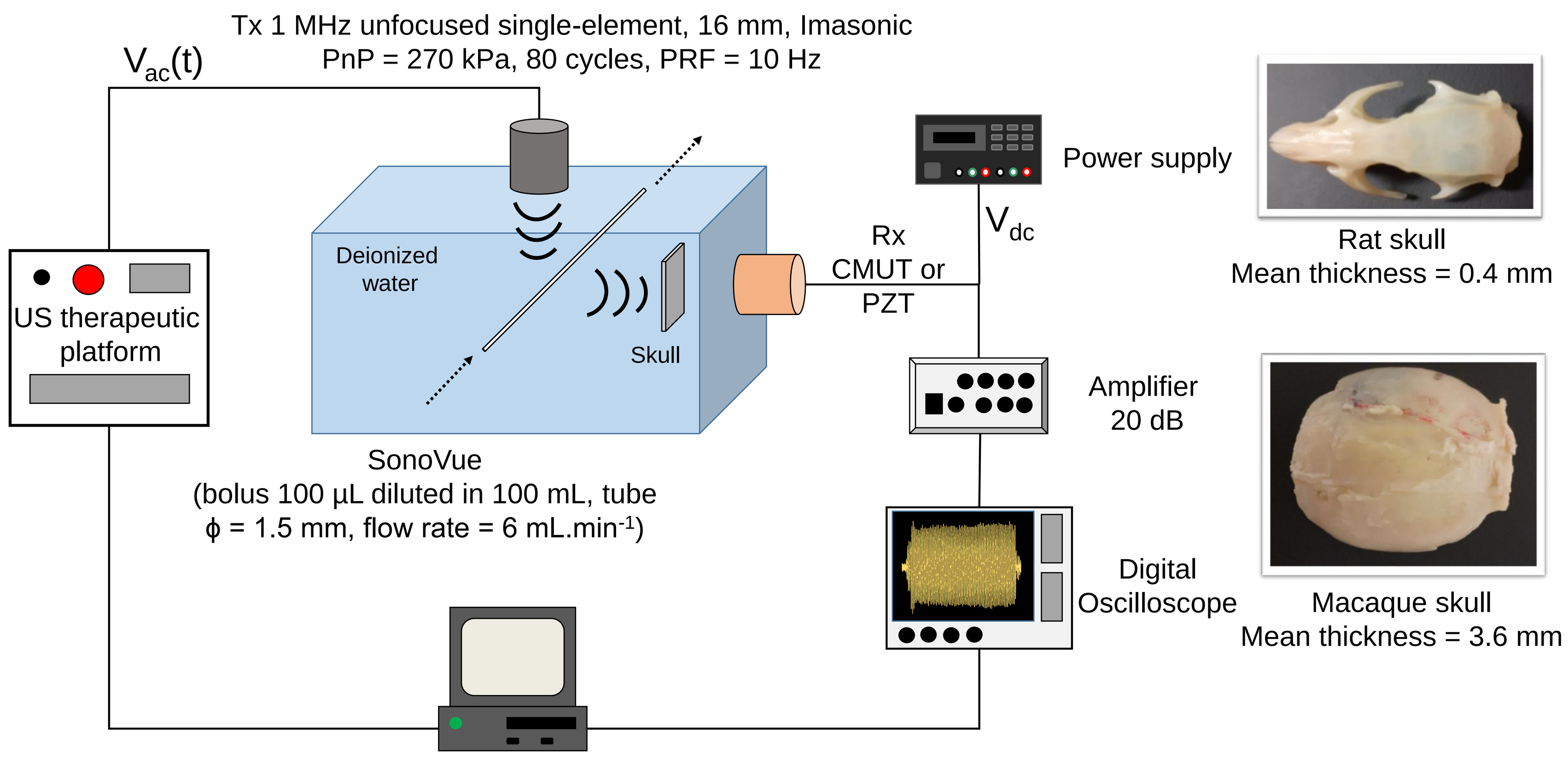
CMUT characteristics

2) CMUT characterization:

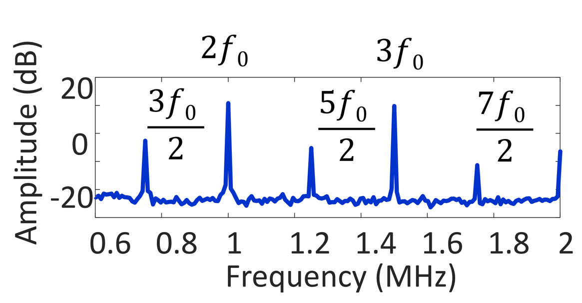
- ***Bandwidth*** with hydrophone (HGL200, ONDA Corp, Sunnyvale, CA) $10V_{pp}$, pulse width=150ns, pulse repetition frequency=100Hz)
- ***Collapse voltage (V_c)*** by varying V_{dc} from 0V to 120V
- ***Limiting frequency at -20dB (LF-20)*** determined on bandwidth measurement
- ***Signal-to-noise ratio (SNR)*** and ***fundamental-to-harmonic ratio (FHR)*** in receive mode as function of the V_{dc} and the acoustic pressure

3) Evaluation of CMUT ability to detect the signal from circulating MB without skull, through rat skull and through macaque skull

Experimental apparatus



The frequency response from circulating MB was evaluated by calculating the area under curve ratio (AUCR) between the signal from MB and the baseline (water only) for harmonic ((n+1)f_0, n=2 to 6) and UH (0.5nf_0).



References:

[1] A. Novell *et al.* "A new safety index based on intrapulse monitoring of ultra-harmonic cavitation during ultrasound-induced blood-brain barrier opening procedures," Sci. Rep. 2020

[2] A. Novell *et al.* "Exploitation of capacitive micromachined transducers for nonlinear ultrasound imaging," IEEE Trans. Ultrason. Ferroelectr. Freq. Control 2009

[3] A. Dauba *et al.* "Evaluation of capacitive micromachined ultrasonic transducers for passive monitoring of microbubble-assisted ultrasound therapies", JASA 2020

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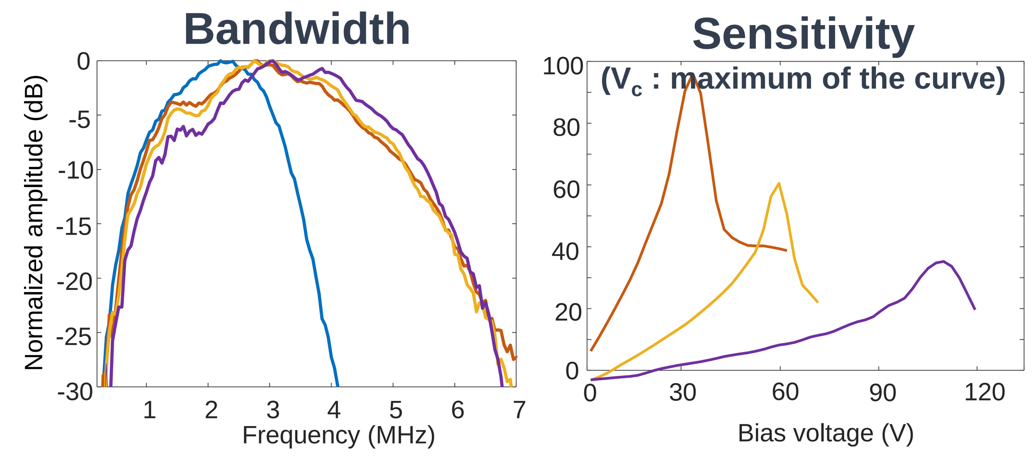
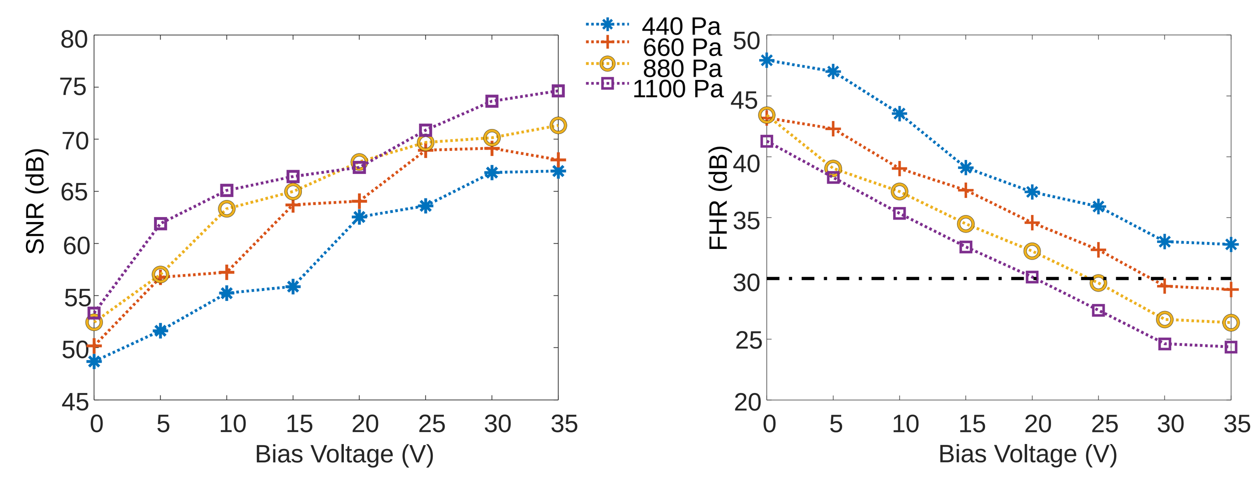
CMUT CHARACTERIZATION

1) Characterization in transmit mode



	Center frequency	*LF-20 (MHz)*	V_c
PZT	2.25MHz	0.5 – 3.8	
$CMUT_{37x37\mu m^2}$	2.7MHz	0.6 – 6.3	35V
$CMUT_{32x32\mu m^2}$	3.0MHz	0.6 – 6.3	60V
$CMUT_{27x27\mu m^2}$	3.2MHz	0.6 – 6.3	110V

2) Characterization in receive mode

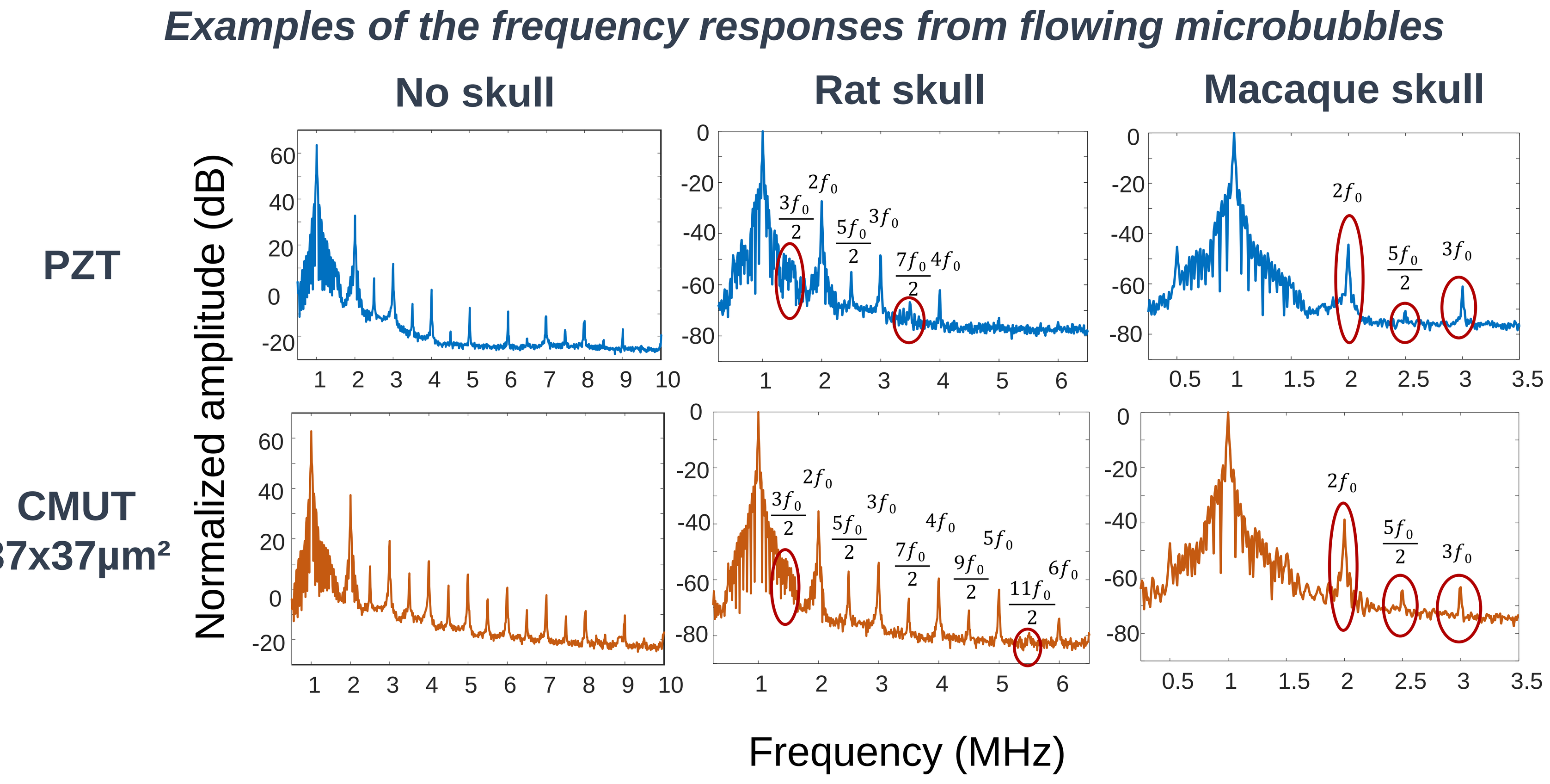


Variation of the SNR and the FHR as a function the bias voltage and the acoustic pressure applied at 1 MHz for the CMUT 37×37µm²

→ In order to **avoid the CMUT intrinsic nonlinearity** as it could mask MB response all CMUT configurations were used at **V_{dc} = 0.6 V_c** in order to maximize the sensitivity in receive mode while maintaining a reasonable level of nonlinearity (**FHR > 30 dB**[2]).

DETECTION OF CIRCULATING MB SIGNAL

Examples of the frequency responses from flowing microbubbles



The skull considerably attenuates the high frequency components

PCD transducer	***AUCR Subharmonic 0.5 f_0 (dB)***	***AUCR Harmonic (3 f_0 to 6 f_0) (dB)***	***AUCR Ultraharmonic (2.5 f_0 to 5.5 f_0) (dB)***	***AUCR Broadband (dB)***
PZT 2.25 MHz	11.3 ± 2.1	18.5 ± 2.2	20.0 ± 2.1	3.4 ± 0.5
CMUT 37×37 µm²	9.7 ± 1.4	24.2 ± 4.5	41.7 ± 5.2	5.2 ± 1.5
CMUT 32×32 µm²	10.3 ± 1.4	18.3 ± 3.3	37.7 ± 3.9	5.1 ± 0.6
CMUT 27×27 µm²	10.3 ± 0.7	23.1 ± 2.0	35.8 ± 0.7	4.4 ± 0.7
AUC ratio through a rat skull n=3				

PCD transducer	***AUCR Subharmonic 0.5 f_0 (dB)***	***AUCR Harmonic (3 f_0) (dB)***	***AUCR Ultraharmonic (2.5 f_0) (dB)***	***AUCR Broadband (dB)***
PZT 2.25 MHz	16.3 ± 3.4	-0.4 ± 1.0	2.4 ± 1.4	-0.2 ± 0.3
CMUT 37×37 µm²	14.4 ± 1.8	-1.8 ± 0.7	7.9 ± 1.2	2.2 ± 0.5
AUC ratio through a macaque skull n=3				

Compared to PZT, the UH signal from MB is increased by 21.7 dB through the rat skull and 5.5 dB for the macaque[3].

DISCUSSION & FUTURE WORKS

✓ While efficient and safe BBB opening can be ensured by intra-pulse monitoring of UH content[1], **this study validates CMUT technology for the monitoring of cavitation-based ultrasound therapies** such as HIFU, sono-permeabilization or BBB opening.

✓ Thicker is the skull bone, more difficult is the detection of high frequency content (as shown in macaque skull data). Usually, lower frequency are used for thick skull such as macaque or human but the detection of high frequency could also be improved by the development of **dedicated amplifiers that can be directly integrated on CMUT PCD.**

✓ The results obtained in this study encourage us in **pursuing our investigation *in vivo* and in developing CMUT-based PCD for large animal validation.** Smaller devices (diameter 7 mm) with membrane dimensions of 32 × 32 µm² and 37 × 37 µm² are currently integrated into therapeutic transducers and evaluated for animal experiments.