

Driving Electronics for Low-Intensity Therapeutic Ultrasound Transducers

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A thesis submitted for the degree of Doctor of Philosophy

DEPARTMENT OF BIOENGINEERING

IMPERIAL COLLEGE LONDON

JANUARY 2024

To my dear husband, and my dear family ...

***"Whoever takes a path upon which to obtain knowledge,
Allah makes the path to Paradise easy for him."***

Hz. Muhammed (S.A.V.)

"I am sending you as sparks, you must return as fire balls."

Mustafa Kemal ATATÜRK

***“Her kim şan ve şeref istiyorsa bilsin ki, şan ve şeref
bütünüyle Allah’a aittir.”***

Fâtır Suresi 10. Ayet

Declaration

Declaration of Originality

I confirm that all the work reported in this thesis is my own, unless stated otherwise. Contributions from collaborators have been clearly indicated and all source material has been appropriately referenced and acknowledged.

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Acknowledgments

First, I would like to thank my supervisor, Dr. James Choi for his support and guidance throughout my PhD. None of this work would have been possible without his help and trust.

Second, I would like to thank all the members of the NSB Lab, both past and present, who I have had the pleasure of working with. Many of them have become close friends of mine and have made this journey enjoyable. A special thank you to Dr. Krit Sujarittam and Dr. Zheng Jiang for offering not only help, but also their friendship from the very start of my PhD. All the experiments in this thesis would not have been possible without the expertise and help of yours. I also would like to acknowledge Dr. Sophie Morse and Dr. Javier Cudeiro who have been supporting and motivating me as close friends and inviting me to their house. A big thank you to Dr. Tiffany Chan for our fruitful discussions and our socials. A big thank you to Dr. James Bezer, Dr. Dani Chattenton, (soon to be Dr.) Shusei Kawara, and (soon to be Dr.) William Lim Kee Chang. I have learnt so much from them and they have provided enormous support. A big thank you to Dr. Antonios Pouliopoulos for answering my questions and sharing his experiences with me. A big thank you to all the students that I have co-supervised and who have helped me with my work.

Third, I would like to thank our collaborators and our amazing technical team for their assistance, suggestions, and help: Paschal Egan, Tariq Malik and Niraj Karnabar for the help and the guidance on electronics.

I would also like to extend my appreciation to Republic of Türkiye Ministry of National Education for their financial support during my PhD studies.

Last, I would like to thank all my friends and family (my father Züfer İlbilgi, my mother Huri İlbilgi, my sisters Melek İlbilgi Altındağ & Melike İlbilgi Filik, and my brother Mert İlbilgi), your constant support has been invaluable. A special thanks to my husband Ahmet Serhat YILDIZ who always believes in me, stands by me, for his constant support and love.

Abstract

In therapeutic ultrasound, an array of transducers can be used to focus and steer an ultrasound beam, allowing several localised regions in the body to be treated. An electronic driving system coordinates the emission from each of the array's transducers to achieve steering and constructive interference at the target location. However, imaging or thermal ablation-focused design of commercially available multi-channel arrays and their drivers renders them unsuitable (higher frequency range $>1\text{MHz}$) or prohibitively expensive (costs $>\$100000$) for other therapeutic applications, such as microbubble-based methods. This project aimed to design a cost-effective ultrasound system for low-intensity microbubble-based therapeutic ultrasound applications.

First a low-complex, affordable single-channel driver that could be used in driving arrays with high element counts was designed. Two digital signals from a microcontroller (0–3.3V) were used to control the amplitude and frequency of the single-channel driver. The results of the single-channel driver showed that the driving circuit was tuneable in the frequency range of 0.1–1 MHz and producing short pulses with amplitudes between 0–150 V. Then our system was scaled into an 8-channel driver and then a 16-channel driver to drive dome-shaped multi-channel arrays. Coupled with the custom arrays, electronic beam steering and focusing were demonstrated. The system is effective and affordable for therapeutic ultrasound arrays with higher element counts. The overall cost of a 128-channel driver circuit was estimated to less than \$1600, excluding the power supply and the control unit.

Finally, a dynamic matching network was designed to improve the effectiveness of therapeutic ultrasound systems while offering a cost-efficient option for matching networks implemented with multiple frequencies. Experimental results demonstrate the effectiveness of the dynamic matching network in improving peak-negative pressure (PNP) from 66.6 % to 422.52 % for different transducers and frequencies.

Table of Contents

Declaration	5
Acknowledgments.....	6
Abstract	7
Table of Contents	8
List of Figures	12
List of Tables	17
Abbreviations.....	19
Publications	22
1 Introduction	23
1.1 Diseases related to brain	23
1.2 Addressing the challenge of crossing the blood-brain barrier.....	24
1.2.1 Invasive methods	24
1.2.2 Non-invasive methods.....	25
1.3 Focused ultrasound in conjunction with microbubbles to facilitate delivery of drugs to the brain.....	26
1.3.1 Ultrasound	28
1.3.2 Microbubbles in therapy	32
1.3.3 Microbubble Dynamics	33
1.3.4 BBB disruption mechanism with focused ultrasound and microbubbles	
35	
1.3.5 Ultrasound parameters used in therapeutic applications	36
1.3.6 Ultrasound systems used in clinical trials	38
1.4 The transmission and reception of ultrasound wave.....	41
1.4.1 Ultrasound transducers.....	41
1.4.2 Driving/ Acquisition electronics for ultrasound transducers	43

1.5	Thesis aims	45
1.6	References	45
2	A low-cost and scalable single-channel high-voltage driver for therapeutic ultrasound transducers	58
2.1	Introduction	58
2.2	Aims and objectives	61
2.3	Materials and methods	62
2.3.1	Single-Channel Driver Design	62
a)	High-voltage pulser design	62
2.3.2	Electrical characterization	66
2.3.3	Acoustic characterization	66
2.3.4	Microbubble excitation and reception	67
2.4	Results	70
2.4.1	Electrical characterization	70
2.4.2	Acoustic characterization	71
2.4.3	Microbubble excitation and simultaneous reception of microbubbles..	73
2.5	Discussion	74
2.5.1	Single-channel driver	74
2.5.2	Electrical characterization	75
2.5.3	Acoustic characterization	75
2.5.4	Microbubble excitation and reception	76
2.5.5	Integrating into a multi-channel driver	76
2.5.6	Limitations	77
2.6	Conclusion	77
2.7	References	78

3	The design and optimization of a multi-channel low-intensity therapeutic ultrasound driver	84
3.1	Introduction	84
3.2	Multi-element arrays for low-intensity ultrasound	87
3.3	Aims and objectives	87
3.4	Materials and methods	88
3.4.1	8-Channel high-voltage driver system	88
3.4.2	Digital control unit.....	90
3.4.3	16- Channel high-voltage driver system	91
3.4.4	Electrical characterization.....	94
3.4.5	Acoustic characterization: individual-channel characterization	94
3.4.6	Acoustic characterization: electronic beam focussing and steering	95
3.5	Results	97
3.5.1	Electrical characterization: individual-channel characterization	97
3.5.2	Acoustic characterization: individual-channel characterization	99
3.5.3	Acoustic characterization: overall waveform, electronic beam focussing and steering.....	100
3.6	Discussion	103
3.6.1	Electrical characterization.....	103
3.6.2	Acoustic characterization.....	105
3.7	Conclusion.....	106
3.8	References	107
4	The design and optimization of a programmable/dynamic network	113
4.1	Introduction	113
4.1.1	Determining the equivalent circuit models for transducers and simulation tools.....	115

4.1.2	Electrical Impedance Matching Methodologies	117
4.2	Aims and objectives	118
4.3	Materials and methods	118
4.3.1	Complex impedance measurements of ultrasound transducers	119
4.3.2	Designing a programmable/dynamic matching network	119
4.3.3	Experimental Setup for testing the dynamic matching network	123
4.4	Results	124
4.4.1	Different transducers' fundamental frequency matching	124
4.4.2	Harmonic frequency matching of a single transducer	127
4.5	Discussion	130
4.6	Conclusion.....	131
4.7	References	132
5	Conclusion and future outlook.....	137
6	Appendix.....	140

List of Figures

Figure 1.1. Schematic representation of the structural elements of the blood-brain barrier. The blood-brain barrier controls the movement of compounds between the blood and the brain, both via the spaces between cells (paracellular transport) and across the cells themselves (transcellular transport). This diagram is based on a figure from T. Chan's thesis [6].	23
Figure 1.2. Routes of administration for protein therapies targeting the central nervous system (CNS). Initial methods of central nervous system (CNS) protein delivery involved typical administration through parenteral injection, specifically via intramuscular, intravenous, and subcutaneous routes. In such instances, proteins are finally disseminated throughout the systemic vasculature, including the capillaries in the brain. Hence, the delivery of proteins into the brain after parenteral delivery necessitates passing the blood-brain barrier. Central administration methods, such as intraparenchymal and intracerebroventricular, enable bypassing the blood-brain barrier. Intrathecal administration has been employed as a less intrusive substitute for central administration. The intranasal route has lately been investigated as a less invasive delivery technique that enables breaking the blood-brain barrier. Redrawn from [8].	24
Figure 1.3. A visual representation of disrupting the BBB using focused ultrasound and microbubbles. This technique involves the direct injection of microbubbles into the bloodstream, followed by their exposure to focused ultrasound waves. This causes the microbubbles to oscillate radially and apply mechanical pressure on the walls of the blood vessels, leading to an increase in permeability.	27
Figure 1.4. Longitudinal wave. Sound is a wave that propagates longitudinally, characterised by alternating compressions and rarefactions. The compression phase of a sound wave is characterised by high pressure, while the rarefaction phase is associated with low pressure.	29
Figure 1.5. The given diagram illustrates the time-domain ultrasound pressure across the given waveform. 1) Peak negative pressure refers to the maximum magnitude of negative acoustic pressure generated throughout a single cycle of ultrasound. 2) Pulse length refers to the time duration of an ultrasonic pulse train. 3) Frequency refers to the number of acoustic pressure cycles occurring per unit of time during the execution of ultrasound. 4) The time between pulses refers to the duration between pulses which is also inversely proportional to the pulse repetition frequency (PRF).	31
Figure 1.6. Diagram of a single-element transducer. A single-element transducer comprises a PZT disk together with a matching and a backing layer.	43
Figure 1.7. A complete single-element ultrasound driving, and acquisition system used in pulse-echo mode consists of a signal generator, amplifier, T/R switch, preamplifier, and oscilloscope.	43
Figure 1.8. Transmit beam (a) focussing, (b) steering. The time delay associated with electrical excitations across various elements is employed to synchronize the arrival of ultrasonic waves generated by different transducers at a certain location. The method of altering the focal location is commonly referred to as steering. It should be noted that this method applies not only to linear arrays but also to other types of arrays such as dome-shaped arrays.	44

Figure 2.1. Design overview of the proposed single-channel driver. A single-channel driver system contains a high-voltage pulser (HV) design, a matching network, and a high-voltage switch.....	62
Figure 2.2. Single-channel high-voltage square wave pulse generator (HV Pulser). (a) A digital control unit (not shown here) dictates the amplitude via the amplitude control signal input (0-3.3 V) and the centre frequency, pulse length, and phase via the frequency control signal (0-3.3 V). (b) A populated printed-circuit board (PCB) of the design.....	63
Figure 2.3. Electrical characterization experimental setup. The experimental setup was used to test the performance of the high-voltage pulser. The pulser was tested by using a high-impedance probe for different frequencies, number of cycles, and amplitude.	66
Figure 2.4. Acoustic performance of single-channel driver. The experimental setup was used to evaluate the single-channel driver's performance with different transducers for frequencies at (a) 1 MHz, (b) 0.5 MHz, and (c) 0.3 MHz. Acoustic signals were captured by a 1mm needle hydrophone, digitized with an oscilloscope, and stored on a computer.	67
Figure 2.5. 3D printed wall-less channel frame [39].	68
Figure 2.6. Experimental setup for microbubble excitation and reception of cavitation signal. Microbubbles were flowing inside a 100 μm diameter channel and a 1 MHz focussed transducer was excited by a single channel driver which was controlled by 2 function generators connected to a computer. The cavitation signals were collected by transducer using a high-voltage protection switch and digitized before being recorded by a computer.	69
Figure 2.7. Electrical behaviour testing for duty cycle vs output amplitude. Single-channel driver output was measured with a high-impedance probe when the low-pass filter was not connected. The duty cycle varied from 5 % to 95 % with the increment of 5 and the final output measured at 99 %.	70
Figure 2.8. Electrical behaviour testing for different settings. Waveforms produced from the single-channel driver for different settings: amplitudes of 40 V (a), 75 V (b), 145 V (c); number of cycles of 1 (d), 5 (e), 10 (f); frequencies of 0.5 MHz (g), 0.75MHz (h), 1MHz (i).	71
Figure 2.9. Acoustic testing to observe the effect of the matching on the output signal. Waveforms were generated by a single PZT transducer which was excited with 3 cycles, 0.5 MHz, and 95% duty cycle (approximately 150 Vpp) by a single-channel driver. Acoustic emissions from the transducer were captured by a 1-mm needle hydrophone. The captured waveforms time-domain (a), (c) and frequency domain (b), (d) without a low-pass filter and (c), (d) with a low-pass filter connected (a), (b).	72
Figure 2.10. Acoustic testing for evaluating the performance of the single-channel driver with different transducers and their corresponding pressure vs duty cycle responses. Waveforms were generated by three different transducers (0.3 MHz, 0.5 MHz, and 1 MHz) which were excited with 10 cycles. Acoustic emissions from the transducer were captured by a 1-mm needle hydrophone. The captured waveforms in the time domain at 95 % duty cycle excitation (a, b) and 70 % duty cycle excitation (c). Duty cycle vs pressure output plotted for 0.3 MHz (d), 0.5 MHz(e), and 1 MHz (f).	73

Figure 2.11. Received microbubble signals from the 1 MHz focussed PZT transducer. 1 MHz focussed transducer was excited with 5 cycles at 0.5MPa and positioned 6.8cm away from the wall-less channel. Received microbubble signals in the time domain (a), and in the frequency domain (b).....	74
Figure 3.1. Single-channel high-voltage square wave pulse generator (HV Pulser). (a) A digital control unit (not shown here) dictates the amplitude via the amplitude control signal input (0-3.3 V) and the centre frequency, pulse length, and phase via the frequency control signal (0-3.3 V). (b) A populated printed-circuit board (PCB) of the design.	88
Figure 3.2. Structure of the eight-element array frame. (a) the lateral perspective of the dome-shaped array frame. (b) The frontal perspective of the array consists of 8 elements.....	89
Figure 3.3. The 8-channel driver. Single-channel high-voltage pulsers were connected with a stripboard for DC supply distribution. Each channel was connected to a 120 μ H inductor for matching.	90
Figure 3.4. Digital control PCB for sixteen-channel excitation. One master board, one slave board for amplitude control, and 16 slave boards for frequency control were employed.	91
Figure 3.5. Structure of the sixteen-element array frame. (a) the lateral perspective of the dome-shaped array frame. (b) The frontal perspective of the array consists of 16 elements.....	92
Figure 3.6. Sixteen-channel high-voltage square wave pulse generator (HV Pulser) populated on a printed circuit board (PCB).	92
Figure 3.7. Sixteen-channel matching network with T/R switch populated on a printed circuit board (PCB).	93
Figure 3.8. The complete 16-channel driver system with 16-element array. The 16-channel driver generated excitation that went through the 16-channel matching network before reaching the PZTs to generate ultrasound. The parameters for the excitation signal were sent through MATLAB via the digital control unit. .	93
Figure 3.9. Experimental setup for electrical characterization. Each channel was tested in the 8-channel high-voltage driver system and 16-channel high-voltage driver system without a transducer connected as a load. Two function generators were used to control the amplitude and the frequency/delays/number of cycles of the signal. The generated square waves in different settings were observed by using a high-impedance probe, and data was collected by an oscilloscope. The duty cycle of the amplitude control signal was varied from 5% to 99% for four different frequencies namely 0.1 MHz, 0.3 MHz, 0.5 MHz, and 1 MHz. All of the channels were tested individually in the same way.....	94
Figure 3.10. Experimental setup for evaluating the performance of each channel driving a single transducer (a) with a matching network connected and (b) without a matching network connected. The 1-mm hydrophone was placed 15 cm away from the transducer. The PZT transducer was excited by our high-voltage drivers from 8-channel and 16-channel drivers controlled with a digital control unit. The generated ultrasound field was measured by a needle hydrophone. The received signals were digitized before being stored on a computer. The performance of all 16 channels was tested on the same setup.....	95

Figure 3.11. Experimental setup for characterising electronic beam focussing and steering with an (a) 8-element and (b) 16-element system. (a) An 8-channel driver made of eight single-channel drivers was used to drive an in-house-built 8-element array. (b) A 16-channel driver was used to drive an in-house-built 16-element array. Ultrasound pulses were captured with a 1-mm-in-diameter needle hydrophone fixed on a 3D-positioning system located 15 cm away from the array.(Array and array elements designed by a former PhD student, Zheng Jiang).....	97
Figure 3.12. Electrical testing revealed the output voltage vs duty cycle relationship for individual drivers of (a) an 8-channel system and (b) a 16-channel system. The duty cycle was varied from 5 to 99% and frequency was varied from 0.1 to 1 MHz without a matching network connected.	98
Figure 3.13. The performance of the digital control unit. The output of the digital control unit was captured with an oscilloscope for different (a) numbers of cycles (b) frequencies (c) delays and (d) duty cycles.....	98
Figure 3.14. Acoustic testing demonstrated the output pressure vs duty cycle relationship for each of the (a, b) 8 single-channel drivers and (c, d) 16-channel drivers. A PZT transducer was excited in a water tank by each channel applying a 0.5 MHz and 5-cycle pulse both (a, c) without and (b, d) with a matching network connected. Ultrasound pulses were captured with a 1-mm-in-diameter needle hydrophone fixed on a 3D-positioning system located 15 cm away from the transducer's surface. All 8 channels and 16 channels were tested individually using the same transducer.....	99
Figure 3.15. The relationship between the PNP and the duty cycle of the 16-element array driven by the 16-channel driver. A needle hydrophone was placed at the geometric centre of the 16-element array. The duty cycle used to control the 16 drivers was adjusted between 10% and 90%, which increased the PNP at the focus.	101
Figure 3.16. Beam profile for the 8-channel driving circuit with an 8-element array. Using the 8-channel driver to drive an 8-element ultrasound array, a focal beam could be formed (a) at the geometric focus and (b) at 5-mm away from the geometric focus along the x-axis. Beam steering was performed by applying time delays using the 8-channel driving circuit. Beam profile measurements were performed using a 1-mm-in-diameter needle hydrophone with a raster scan.	101
Figure 3.17. Beam profiles of 16-element array when focusing and steering on the x-axis. Beam profiles at the (c), (f) geometry focus and when the focus was steered along on the x-axis by (b), (e) 5 mm and (a), (d) 10 mm.	102
Figure 3.18. Beam profiles 16-element array steering the focus on the z-axis. Beam profiles when the focus was at (c), (f) geometric centre and when the beam was steered by (b), (e) 5 mm away from the transducer and (a), (d) 10 mm away from the transducer.	103
Figure 4.1. Conjugate matching of input and output impedance via a two-port Electrical Impedance Matching Network.	114
Figure 4.2. Single-frequency Butterworth-Van Dyke (BVD) model for piezoelectric transducer.	116
Figure 4.3. Four different configurations for L-type impedance matching networks were used to cover the entire Smith chart. If the electrical impedance of the driving electronics is smaller than transducer type(a) and type (b), larger than transducer type (c) and type (d) are used.	120

Figure 4.4. Design of a programmable matching network on a PCB.	121
Figure 4.5. The overall structure of the dynamic matching network (c) creates different types of L-networks by adding inductors in series (a) and capacitors in parallel (b) via programmable switches. Capacitors ranging from 1 pF to 10nF connected in parallel with switches allowing a final capacitor value ranging from 1 pF to 99.999 nF with a 1 pF sensitivity (b). Inductor values ranging from 1 nH to 100 μ connected in series to create a final inductor value ranging from 1 nH to 199.999 μH (a).	122
Figure 4.6. Experimental setup for evaluating the performance of the dynamic matching network. The 1 mm hydrophone was placed against the transducer at each transducer's focal point. The programmable/dynamic matching network was connected between the RF amplifier and the transducer. The signals were digitized by an oscilloscope and stored on a computer.	123
Figure 4.7. The photograph of designed and constructed programmable matching network in an experimental setup.	124
Figure 4.8. Fundamental frequency matching for 0.5 MHz transducer. Different matching configurations were tested with the transducer's fundamental frequency with 10 cycles. Signals were captured by a 1mm needle hydrophone. The time domain signals for no matching (a), series inductor (c), type-a matching (e), and type-b matching (g). The frequency spectrum for no matching (b), series inductor (d), type-a matching (f), and type-b matching (h).	125
Figure 4.9. Fundamental frequency matching for 1 MHz transducer. Different matching configurations were tested with the transducer's fundamental frequency with 10 cycles. Signals were captured by a 1mm needle hydrophone. The time domain signals for no matching (a), type-c matching (c), type-b matching (e), and type-a matching (g). The frequency spectrum for no matching (b), type-c matching (d), type-b matching (f), and type-a matching (h).	126
Figure 4.10. 3rd harmonic frequency matching for 1 MHz transducer. Different matching configurations were tested with the transducer's 3rd harmonic frequency with 10 cycles. Signals were captured by a 1mm needle hydrophone. The time domain signals for no matching (a), type-b matching (c), type-c matching (e), and type-d matching (g). The frequency spectrum for no matching (b), type-b matching (d), type-c matching (f), and type-d matching (h).	128
Figure 4.11. 5th harmonic frequency matching for 1 MHz transducer. Different matching configurations were tested with the transducer's 5th harmonic frequency with 10 cycles. Signals were captured by a 1mm needle hydrophone. The time domain signals for no matching (a), type-c matching (c), and type-b matching. The frequency spectrum for no matching (b), type-c matching (d), and type-d matching (f).	129

List of Tables

Table 3.1. Overall design specifications.	89
Table 4.1. Measured impedance values for two different transducers at 3 different frequencies.....	119

List of Equations

(1.1)	28
(1.2)	29
(1.3)	30
(1.4)	30
(1.5)	30
(1.6)	31
(1.7)	34
(4.1)	117
(4.2)	117

Abbreviations

A	AIM	Acoustic Impedance Matching
B	B	Susceptance
	BBB	Blood Brain Barrier
	BJT	Bipolar Junction Transistor
	BVD	Butterworth Van Dyke
C	c	Sound
	CNC	Central Nervous System
	CSF	Cerebrospinal Fluid
	CNS	Central Nervous System
	C	Capacitance
	CMUT	Capacitive Micromachined Ultrasonic Transducers
D	DC	Direct Current
	DAC	Digital to Analogue Converter
	DPPC	Dipalmitoyl Phosphatidylcholine
	DPPE	Dipalmitoyl Phosphatidylethanolamine
	DPPA	Dipalmitoyl Phosphatidic Acid
E	EIMN	Electrical Impedance Matching Network
F	f	Frequency
	F_c	Centre Frequency
	FWHM	Full Width at The Half-Maximum
	FET	Field-Effect Transistor
	FFT	Fast-Fourier-Transform
G	G	Conductance
H	Hz	Hertz
	HIFU	High Intensity Focused Ultrasound
	HV	High Voltage Pulser
I	IA	Impedance Analysers

	IMN	Integrated Microwave Network
L	L	Inductance
M	MI	Mechanical Index
	MRI	Magnetic Resonance Imaging
	MPa	Megapascals
	MHz	Megahertz
	MOSFET	Metal Oxide Semiconductor Field Effect Transistor
N	NDT	Non-Destructive Testing Purposes
P	PA	Power Amplifiers
	PU	Polyurethane
	PNP	Peak Negative Pressure
	PRF	Pulse Repetition Frequency
	PEG	Polyethylene Glycol
	PZT	Lead Zirconate Titanate
	PCB	Populated Printed-Circuit Board
	PCD	Passive Cavitation Detectors
	PDM	Pulse Density Modulation
	PWM	Pulse Width Modulation
	PVDF	Polyvinylidene Fluoride
	P	Pressure Amplitude
	PL	Pulse Length
	Pa	Pascal
Q	Q	Quality Factor
R	RaSP	Rapid Short Pulse
	R	Resistance
S	SARUS	Synthetic Aperture Real Time Ultrasound System
	SNR	Signal to Noise Ratio

T	T/R	Transmit/Receive
U	UARP	Ultrasound Array Research Platform
V	VDS	Voltage Drop Across the Drain-Source
	VNA	Vector Network Analysers
X	X	Reactance
Y	Y	Admittance Magnitude
Z	Z	Magnitude
	Z	Acoustic Impedance
*	λ	Wavelength
	ϕ	Phase Component
	ρ	Density
	θ	Phase

Publications

Journal papers:

Ilbilgi Yildiz B, Jiang Z, Sujarittam K, Hall T, Choi J. A Low-Cost Multi-Channel Driving System for Therapeutic Ultrasound Arrays. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*. (In correction).

Jiang Z, Cudeiro J, **Ilbilgi Yildiz B**, Sujarittam K, Dickinson R, Guasch L, Tang M, Hall T, Choi J. A. An Ultrasound Array of Emitter-receiver Stacks for Microbubble-based Therapy. *IEEE transactions on bio-medical engineering*, vol. PP 10.1109/TBME.2023.3307462. 22 Aug. 2023, doi:10.1109/TBME.2023.3307462

Jiang Z, Sujarittam K, **Yildiz BI**, Dickinson RJ, Choi JJ. Passive cavitation detection with a needle hydrophone array. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*. 2021 Oct 14;69(1):233-40.

Conference papers:

Ilbilgi Yildiz B, Jiang Z, Sujarittam K, Hall T, Choi J. A Low-Cost Multi-Channel Driving System for Therapeutic Ultrasound Arrays. *International Symposium for Therapeutic Ultrasound, Toronto, Canada, June 7-10, 2022*.

Ilbilgi Yildiz B, Jiang Z, Sujarittam K, Hall T, Choi J. A Low-Cost Multi-Channel Driving System for Therapeutic Ultrasound Arrays. *IEEE International Ultrasonics Symposium, Venice, Italy, Oct. 10-13, 2022*.

Ilbilgi Yildiz B, Jiang Z, Sujarittam K, Hall T, Choi J. A Low-Cost Affordable and Scalable Multi-Channel Driving System for Therapeutic Ultrasound Arrays. *International Symposium for Therapeutic Ultrasound, Lyon, France, April 17-20, 2023*.

1 Introduction

1.1 Diseases related to brain

Diseases related to brain, neurological disorders such as Alzheimer's disease and stroke and brain tumours such as glioblastoma, hemangioblastoma, and meningioma, contribute to around 33% of the worldwide disease burden, a proportion that continues to rise as a result of the increase in the elderly population. [1], [2]. Despite numerous efforts to develop a cure for brain-related diseases, many of them still lack a good treatment option [2].

The current treatment options for brain diseases have limited efficacy, mostly attributable to the presence of a blood-brain barrier (BBB). The BBB is a physical, transport, and enzymatic barrier between the bloodstream and the extracellular fluid of the central nervous system (CNS). While the BBB blocks unwanted large molecules and objects such as blood proteins and pathogens from entering the brain, it prevents therapeutic agents from reaching the diseased regions [3]–[5]. In order to treat brain diseases, there is a need to bypass the BBB while minimising harm to healthy tissue.

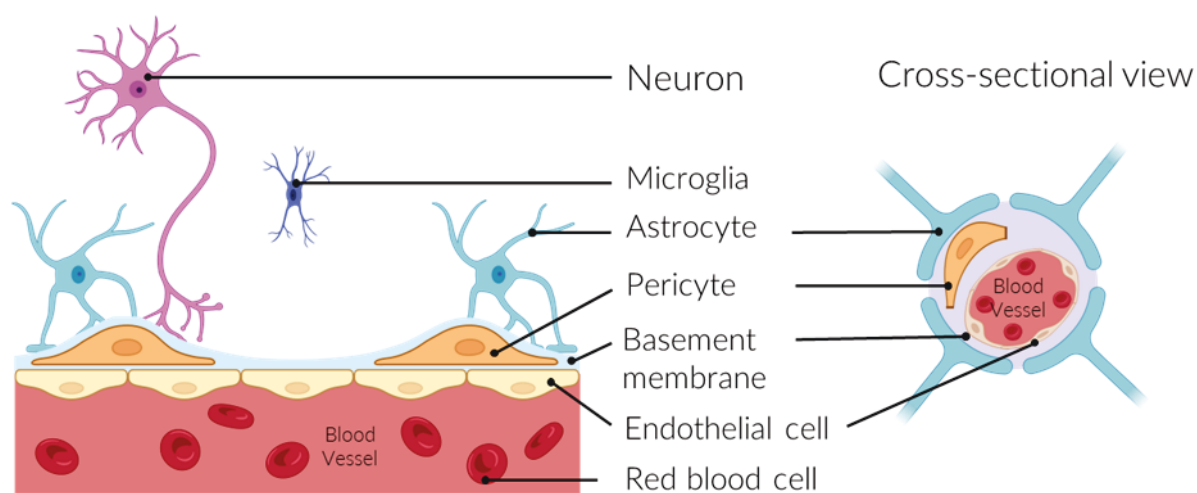


Figure 1.1. Schematic representation of the structural elements of the blood-brain barrier.

The blood-brain barrier controls the movement of compounds between the blood and the brain, both via the spaces between cells (paracellular transport) and across the cells themselves (transcellular transport). This diagram is based on a figure from T. Chan's thesis [6].

1.2 Addressing the challenge of crossing the blood-brain barrier

A variety of approaches have been explored to enhance the delivery of drugs across the BBB. These methods can be divided into two sections: invasive methods and non-invasive methods.

1.2.1 Invasive methods

Invasive methods to overcome BBB include direct injection into the brain parenchyma or into the ventricles [7] and spinal cord injection [8]. The direct injection approach involves the invasive administration of drugs through the skull, resulting in restricted drug penetration beyond the injection site [9]. In order to optimize the distribution of drugs, it is important to administer them with a pressure gradient. Nevertheless, there remains a potential for infection and tissue damage as a result of exposing the brain to the external environment [10]–[12]. The procedure of administering drugs into the spinal cord subarachnoid space through lumbar puncture is known as the spinal cord injection technique [8]. This procedure is less intrusive than the direct injection method, but there are still potential risks of infection and adverse immunological reactions [8], [13].

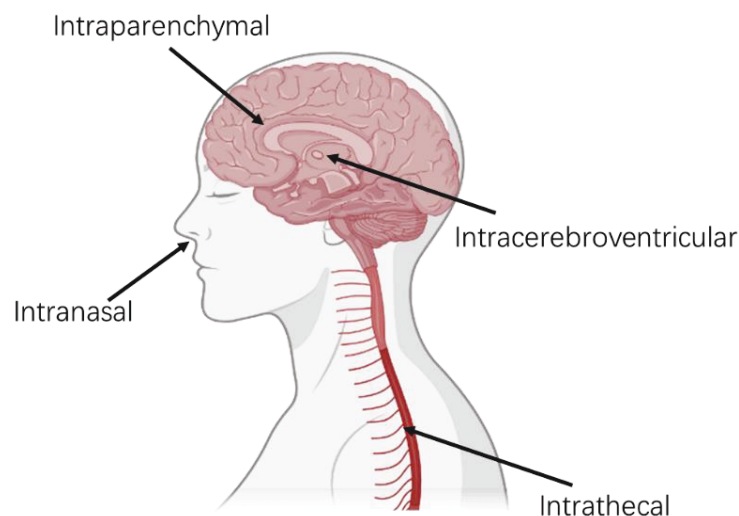


Figure 1.2. Routes of administration for protein therapies targeting the central nervous system (CNS). Initial methods of central nervous system (CNS) protein delivery involved typical administration through parenteral injection, specifically via intramuscular, intravenous, and subcutaneous routes. In such instances, proteins are finally disseminated throughout the systemic vasculature, including the capillaries in the brain. Hence, the delivery of proteins into the brain after parenteral delivery necessitates passing the blood-brain barrier. Central

administration methods, such as intraparenchymal and intracerebroventricular, enable bypassing the blood-brain barrier. Intrathecal administration has been employed as a less intrusive substitute for central administration. The intranasal route has lately been investigated as a less invasive delivery technique that enables breaking the blood-brain barrier. Redrawn from [8].

1.2.2 Non-invasive methods

In the pursuit of safe and non-invasive drug delivery methods to target the brain, several methodologies have undergone extensive investigation. These approaches aim to bypass the need for invasive surgery, offering promising delivery of therapeutic agents to the brain. Here, are some of the key strategies:

1.2.2.1 Intratympanic Delivery

Methods involving the delivery of drugs to the cerebrospinal fluid (CSF) and subsequently into the brain have also been investigated. Intratympanic drug delivery involves the administration of drugs through the inner ear via cerebrospinal fluid. This approach has exhibited the capacity to achieve elevated drug concentrations within the brain in contrast to conventional intravenous administrations. Nevertheless, there remain unresolved questions concerning the overall efficacy of the subject under investigation, as evidenced by prior research studies [14], [15]

1.2.2.2 Osmotic Disruption

Osmotic disruption is a non-invasive technique that focuses on disrupting the BBB temporarily by altering its natural characteristics. Administering hyperosmotic solutions via intravenous injection, this approach increases BBB permeability [16]–[18]. Mannitol, for instance, creates osmotic pressure in capillaries, causing endothelial cells to shrink and junctions to increase leading to an increase in BBB's permeability. This technique can boost the distribution of hydrophilic drugs significantly [18], [19] but is not targeted to specific brain regions and may lead to off-target side effects, such as seizures [20], [21].

1.2.2.3 Delivery Agent Modifications

Another strategy involves modifying drug delivery agents to enhance their effectiveness. This may include reducing molecular weight, altering hydrogen bonding properties, or changing their propensity. While these modifications can be successful, they often prove complex, and

there is no guarantee that medicines will reach therapeutic concentrations in the brain [22]–[25].

1.2.2.4 Intranasal Delivery via Olfactory Pathway

Intranasal delivery has become a viable method for drugs to pass through the blood-brain barrier (BBB) and reach the central nervous system through the olfactory pathway [26], [27]. This method offers advantages such as increased drug concentrations and rapid absorption when compared to intravenous and oral administration. However, regular, and prolonged use of this method can have detrimental effects on the nasal mucosa [28], [29].

1.2.2.5 External Stimulation

Various external stimuli, including microwave exposure [30], [31] and electromagnetic field exposure [32], [33] have demonstrated the ability to transiently modify the permeability of the BBB. These stimuli hold promise for facilitating drug delivery across the BBB but there are safety concerns related to elevated temperatures inside the brain [34], [35].

These diverse methodologies represent innovative approaches to overcoming the challenges of delivering drugs to the brain without resorting to invasive surgical procedures. While each method has its strengths and limitations, they collectively offer a spectrum of possibilities for advancing drug delivery to the brain and improving treatment outcomes for neurological conditions.

1.3 Focused ultrasound in conjunction with microbubbles to facilitate delivery of drugs to the brain

Over the course of the last twenty years, the application of focused ultrasound in combination with microbubbles has evolved as a non-invasive and targeted approach for transiently disrupting the blood-brain barrier by increasing its permeability [36], [37].

Microbubbles are administrated intravenously into the blood circulatory system and the generated ultrasound focussed on the targeted area in the brain. The microbubbles exposed to ultrasound sonication will undergo oscillation, resulting in mechanical stimulation of the surrounding tissues within the region of focused ultrasound. This mechanical stimulation leads to a temporary increase in the brain drug delivery.

For BBB disruption via focussed ultrasound in clinical trials and animal research, long pulses are mostly used to excite the microbubbles. However, a recent clinical investigation has

demonstrated the existence of possible microhaemorrhages, which are visible as hypointense spots on T2 MRI images, by utilizing millisecond-long pulses in human subjects [38].

Additionally, it typically takes between 4 to 48 hours for the blood-brain barrier to regain its normal permeability, as indicated by previous studies [39], [40]. Recent studies have shown that using rapid short pulses can disrupt the BBB temporarily (for less than 10 minutes) while maintaining a uniform and safe delivery [41]. Since the previous studies for the microbubble excitation were based on using long pulses, the hardware used in these studies were also based on long pulses. There are no publicly-available microbubble driving system for short-pulse ultrasound therapy.

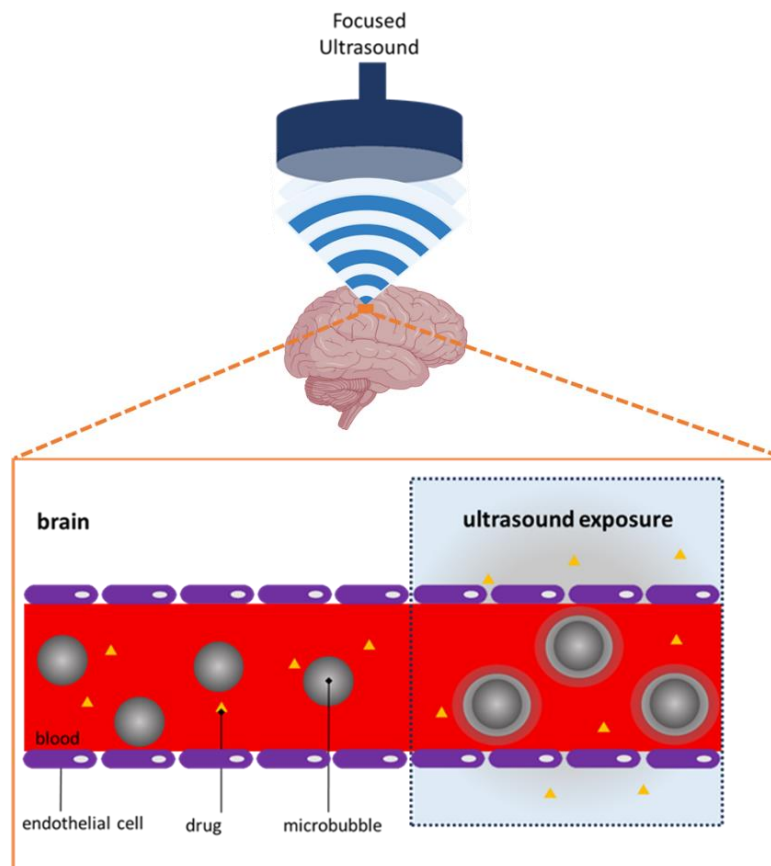


Figure 1.3. A visual representation of disrupting the BBB using focused ultrasound and microbubbles. This technique involves the direct injection of microbubbles into the bloodstream, followed by their exposure to focused ultrasound waves. This causes the microbubbles to oscillate radially and apply mechanical pressure on the walls of the blood vessels, leading to an increase in permeability.

1.3.1 Ultrasound

Ultrasound is a mechanical longitudinal wave characterised by pressure fluctuations, which occur at frequencies above the hearing threshold of human perception (>20 kHz). Ultrasound is used in both diagnostic imaging and non-invasive therapeutic applications [42], [43]. Ultrasound waves are generated by applying an alternating voltage across ultrasonic transducers, which convert electrical energy into acoustic energy through the use of piezoelectric materials. The piezo materials experience rarefaction and compression as a result of electrical stimulation, leading to the generation of pressure waves in the surrounding medium.

In continuous wave (CW) systems, one piezoelectric component transmits constantly ultrasound wave. However, in Pulsed wave (PW) systems, one piezoelectric element transmits and receives alternately.

Ultrasound can be described using various factors, with pressure amplitude (P) being a critical parameter. In many therapeutic ultrasound applications, it is common to characterize the peak negative pressure (PNP) of the ultrasound pulse in the unit of pascal (Pa). Negative pressure is commonly employed because it is the primary method for driving cavitation.

Another significant metric in ultrasound is pulse duration, which refers to the duration of each pulse. Pulse duration is determined by the number of cycles it comprises. In imaging applications, the cycles are usually short, typically less than ten cycles. In contrast, for therapeutic purposes, cycle durations can be much longer, even exceeding one thousand cycles.

Frequency (f) is characterised as the total count of oscillations (cycles) produced by the ultrasound transducer within a single second and is quantified in the unit of hertz (Hz). Period refers to the duration required to complete one cycle. This can alternatively be expressed as the duration between the beginning of one cycle to the beginning of the following cycle. It is important to note that the period and frequency of a wave are inversely related to each other.

$$f = \frac{1}{T}$$

(1.1)

The large variety of frequencies present in short imaging pulses is a result of the time-bandwidth product. Consequently, the centre frequency (f_c) is often used as the primary parameter, as opposed to f . In imaging applications, the centre frequency is $>2\text{MHz}$.

Likewise, the wavelength can be defined as the distance between consecutive peaks of a wave. Differentiating between period and wavelength (λ) is essential as the former refers to length of time while the latter refers to distance. Wavelength can be represented as:

$$\lambda = \frac{c}{f}$$

(1.2)

The velocity of sound (c) in a given medium relies on both the density and elasticity of the material. In particular, an increase in stiffness or density results in an increase in the speed of sound. The speed of sound in soft tissue ranges from roughly 1430 m/s in breast tissue to 1647 m/s in muscle [44], and in water, $1480\text{--}1490\text{ m/s}$ at room temperature ($20\text{--}22\text{ }^\circ\text{C}$) [45].

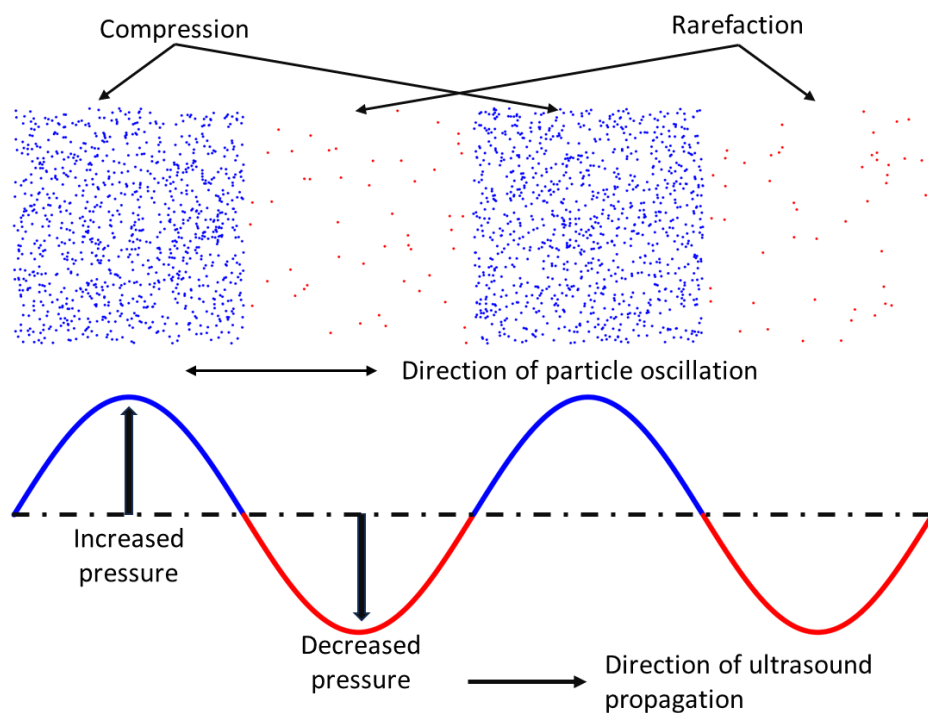


Figure 1.4. Longitudinal wave. Sound is a wave that propagates longitudinally, characterised by alternating compressions and rarefactions. The compression phase of a sound wave is characterised by high pressure, while the rarefaction phase is associated with low pressure.

Ultrasound waves contain a phase component (φ) that indicates the position of the wave during its cycle. The emission of these waves occurs in a pulsed manner, characterised by a pulse length (PL). The pulse length is determined by multiplying the wavelength of the wave by its total number of cycles.

$$PL = \lambda . \text{Number of cycles} \quad (1.3)$$

The pulse repetition frequency (PRF) refers to the frequency at which pulses are emitted, and the duty cycle represents the percentage of time during which ultrasound is being generated [46].

The mechanical index (MI), a commonly employed statistic in medical ultrasound, is a metric that incorporates both pressure and frequency. The definition of the MI is the ratio between the peak rarefactional excitation pressure, measured in megapascals (MPa), and the square root of the excitation centre frequency, measured in megahertz (MHz).

$$MI = \frac{PNP}{\sqrt{fc}} \quad (1.4)$$

The mechanical index is a measure used to assess the probability of non-thermal bioeffects resulting from ultrasonic exposure. It is particularly useful as a predictor of cavitation events in tissue, which may result in biological damage [47].

Sound reflects when it reaches a boundary between materials that have different acoustic impedances. The acoustic impedance (Z) can be mathematically expressed as the product of the density (ρ) and the speed of sound (c).

$$Z = \rho c \quad (1.5)$$

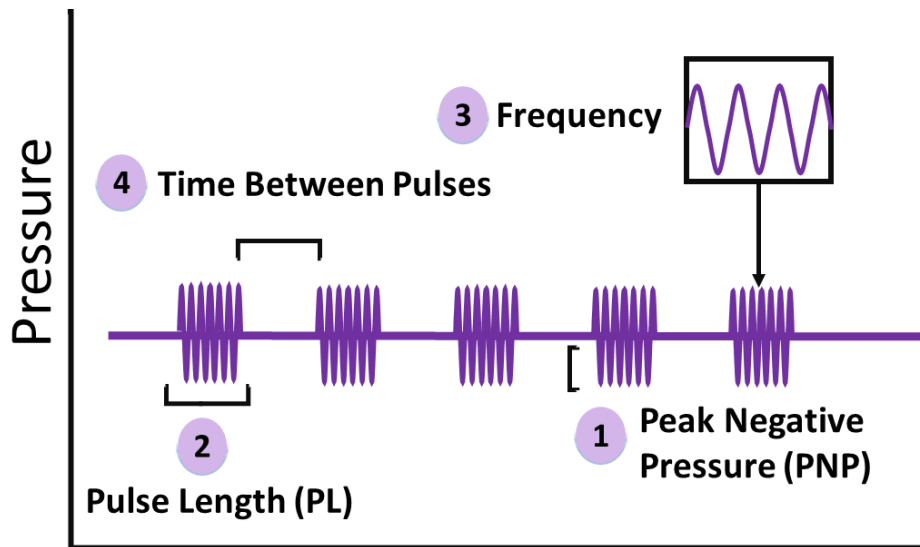


Figure 1.5. The given diagram illustrates the time-domain ultrasound pressure across the given waveform. 1) Peak negative pressure refers to the maximum magnitude of negative acoustic pressure generated throughout a single cycle of ultrasound. 2) Pulse length refers to the time duration of an ultrasonic pulse train. 3) Frequency refers to the number of acoustic pressure cycles occurring per unit of time during the execution of ultrasound. 4) The time between pulses refers to the duration between pulses which is also inversely proportional to the pulse repetition frequency (PRF).

Ultrasound is reflected as it passes through different materials because of the mismatch in acoustic impedance.

$$R = \frac{(Z_1 - Z_2)^2}{(Z_1 + Z_2)^2}$$

(1.6)

The sound propagation is symmetrical regardless of whether it is going from medium 1 to medium 2 or vice versa. The fraction R reflected increases in proportion to the difference in acoustic impedance. The fraction of transmitted sound waves increases as the difference in acoustic impedance decreases [48].

As ultrasonic waves propagate through the human body, their amplitude diminishes as energy dissipates. This phenomenon, referred to as attenuation, occurs as a result of various physical processes, namely scattering, absorption, refraction, reflection, and diffraction taking place within the medium. Refraction and reflection phenomena occur at the boundaries of tissues, whereas absorption and scattering phenomena occur within the tissue

itself. Scattering of sound can occur when it interacts with sub-wavelength particles, such as microbubbles, present in the tissue. [49]. When ultrasound propagates in soft tissue, the primary cause of attenuation is absorption, wherein energy is transformed into thermal energy. The attenuation has a direct relationship with the frequency of sound, whereby higher frequencies experience a greater degree of attenuation compared to lower frequencies. Therefore, the selection of frequency is important in medical applications. In terms of imaging applications, it is essential to achieve an accurate balance between the desired depth of penetration, which necessitates the use of low frequencies, and the desired spatial resolution, which requires the use of high frequencies. In therapeutic applications, it is common to use very low frequencies, often below 1 MHz. This preference arises from the fact that higher frequencies are unable to reach many regions of the body at sufficiently high-pressure amplitudes. For example, focusing on the brain is difficult due to the presence of a thick skull [50]. Refraction occurs when waves pass through interfaces between different media at an angle. The change in velocity of the wave leads to a deviation in the direction of wave propagation. Reflection occurs at the interface between tissues that have different impedances. A portion of the wave will persist in propagating further into the body, while another portion will undergo reflection back towards the ultrasonic transducer. Finally, diffraction is a phenomenon in which a sound wave spreads out as it propagates through an opening or an obstacle.

1.3.2 Microbubbles in therapy

Microbubbles when combined with focussed ultrasound can increase the permeability of the BBB. The most widely used agents consist of a gas core that is encased in a protein or lipid shell. They have diameters ranging from 0.5 to 10 μm , allowing them to move freely through the blood vessels. This characteristic allows them to traverse blood vessels, including capillaries, which have an average diameter of about 7 μm in humans [51], [52]. The capability of microbubbles to travel through capillaries holds significance in therapeutic applications, as it enables the delivery of drugs to the brain over an extensive capillary network spanning a distance exceeding 600 kilometres. [53]. To achieve effective delivery of drugs to specific parts of the brain, microbubbles must increase the permeability of capillary vessels.

These microbubbles are readily accessible in the market and are used as contrast agents for ultrasound imaging [54]–[56]. The gas core of these microbubbles serves as an effective scatterer of ultrasonic waves, enhancing imaging by producing signals significantly stronger than those originating from tissue[57], [58].

Commercially available microbubbles that are frequently used in many applications, such as Definity and SonoVue contain phospholipid shells that are equipped with poly(ethylene glycol) (PEG) brushes [54], [55], [59], [60]. These PEG brushes serve the purpose of preventing coalescence and extending the half-life of these microbubbles [61].

In-vitro investigations often offer a controlled setting for assessing the stability of microbubbles. The duration of microbubbles' decay can vary considerably based on their composition, size, and the surrounding medium. For instance, Definity has a half-life of around 15 to 20 minutes in a standard vitro setup whereas SonoVue has a half-life of around 6 to 8 minutes. In-vivo stability of microbubbles is frequently reduced because of the complex interactions with the biological environment, which involve clearance by the immune system and other physiological processes. SonoVue microbubbles in human blood circulation has a half-life around 2 to 4 minutes [62]. Definity microbubbles have longer circulation half-lives (4.98–6.88 min) [63].

1.3.3 Microbubble Dynamics

When exposed to an ultrasonic field, microbubbles exhibit a variety of dynamic behaviours, including pulsation, collapse, dissolution, fragmentation, microjetting, translation, and other structural changes. A microbubble's activity is greatly influenced by a variety of elements, including ultrasonic parameters, microbubble properties, and the surrounding environment. A microbubble's actions can produce a diverse set of biological responses in the surrounding tissue. All of these factors must be considered while constructing microbubble-based therapy.

Microbubbles are sensitive to acoustic pressure fluctuations. Microbubbles expand and collapse in response to the wave's rarefactional and compressional phases, respectively. Acoustic cavitation is the term for this type of behaviour. The inertia of the surrounding liquid, surface tension, the internal gas pressure, and the ultrasonic pressure are some of the key elements determining the volumetric oscillation of microbubbles [64].

The oscillation of microbubbles is mostly induced by ultrasonic pressure when exposed to low pressures. This allows microbubbles to fluctuate around an average radius, a process known as non-inertial cavitation [65]. The amplitude of the radial oscillations of the microbubble increases with the magnitude of the external force applied until the inertia of the surrounding fluid becomes the predominant driving force over other factors. [66]. When this occurs, the microbubbles undergo inertial cavitation[67]. This mechanism's oscillatory behaviour is defined by a large increase in radius, followed by a rapid and powerful collapse, facilitated by the liquid's inertia. The gas core's rapid compression can generate shock waves and raise temperatures [65], [68]. Stable cavitation refers to oscillations that are recurrent over several ultrasound cycles, which can occur for both non-inertial and inertial cavitation. Transient cavitation refers to short-lived activity [69]. Several aspects determine the threshold for inertial cavitation, including the initial size of the microbubble, its gas composition, the qualities of the surrounding medium, surface tension, and the centre frequency of the produced ultrasound. Surface tension acts as a restoring force that resists deformation of the microbubble. When a microbubble undergoes volumetric oscillations, its surface area changes. Surface tension strives to minimize this surface area, creating a force that opposes the expansion or contraction of the bubble. This restoring force is central to the oscillatory behaviour of the bubble.

However, not all phenomena observed in microbubbles can be attributed only to volumetric oscillations. Acoustic radiation forces, also known as translational forces, are experienced by microbubbles during ultrasound exposure [70]. When sound waves interact with a material, they exert a translational force on the substance in the same direction as the wave's propagation. The cause of this phenomenon is the steady decrease in the strength of sound as it propagates, resulting in energy dissipation. In the context of radiation force or elasticity imaging, the force described below is the principal mechanism responsible for creating tissue displacements.

$$\mathbf{F} = -V(t)\nabla P \quad (1.7)$$

represents the force exerted on a particle within a pressure wave. The variable $V(t)$ denotes the dynamic volume of the bubble as it changes with respect to time. When bubbles are

present in an unconfined fluid, they experience a translational force when exposed to an ultrasound field. When averaged across an acoustic cycle, this force is not equal to zero. The primary radiation force is the name given to this phenomenon. Ultrasound can be characterised as an oscillating wave with a zero average over-time slope of the pressure wave, despite the lack of attenuation. However, due to the variability in bubble volume during the cycle, the product of these factors can have a non-zero value. The propagation direction of the ultrasonic wave is aligned with the direction of microbubble motion induced by the primary radiation force [65], [70].

Secondary radiation forces are applied to microbubbles in close proximity. This effect occurs due to the emission of sound waves by microbubbles, which subsequently interact with other bubbles in a way similar to the behaviour seen from the incident wave. The interaction between two bubbles can result in secondary radiation forces that can be either repulsive or attractive, based on the respective bubble diameter and the ultrasonic frequency.

1.3.4 BBB disruption mechanism with focused ultrasound and microbubbles

The complete mechanism of the BBB disruption with ultrasound and microbubbles are still unknown. Nevertheless, research has found various potential methods for overcoming this barrier, including transcellular and paracellular pathways [71]–[75]. The transcellular route involves transport via caveolae and cytoplasmic vacuoles [71], [72], [74]. Caveolae are tiny invaginations in the cellular membrane that give form to vesicles in the cytoplasm. These structures have the ability to internalise macromolecules, poisons, and viral infections [76]. Research indicates that ultrasound and microbubbles promote the creation of these vesicles and enhance their ability to move across cells, as demonstrated on both the inner and outer sides of endothelial cells [72]. Furthermore, in addition to caveolae, chemicals that have been labelled and delivered using focused ultrasound have also been observed in vacuoles. Vacuoles are organelles within the cytoplasm that are enclosed by a membrane and filled with fluid.

The observed bioeffects may be due to many potential interactions between microbubbles and the surrounding vasculature. Ultrasound induces the expansion and contraction of microbubbles, and the enlargement of larger bubbles can completely fill the inner space of capillaries, mechanically stretching the walls of the blood vessels. This stretching has the potential to cause the opening and rearrangement of tight junction proteins. Ultrasound-

induced alterations in capillary pressure can impact the blood-brain barrier [77], which may result in biochemical responses such as proinflammatory signals that enhance permeability [78]. Research has demonstrated that the oscillations of microbubbles lead to the narrowing of small arteries called arterioles [75], resulting in decreased blood flow and the temporary restriction of blood supply known as transient ischemia. This condition has been found to promote the process of transcytosis [79], which involves the transport of substances between cell layers. Therefore, vasoconstriction may be a plausible explanation for the observed rise in transcytosis.

An increase in permeability may also result from the displacement of microbubbles against vessel walls caused by the force of the ultrasonic wave (translational motion) or the movement of the fluid around them as the microbubbles oscillate. Microbubbles may also undergo collapse under the influence of sonication, resulting in the creation of concentrated shock waves and fluid jets that apply forces to the walls of the vessel. The extent to which BBB permeability increases also depends on the size of the microbubbles. Microbubbles with a diameter similar to capillaries may experience improved permeability without the need for inertial cavitation, but smaller bubbles may require it [80]. Moreover, vascular bifurcations frequently experience heightened permeability, potentially as a result of the accumulation or entrapment of microbubbles in these regions [75].

1.3.5 Ultrasound parameters used in therapeutic applications

Since the 1960s, ultrasound has been extensively used in the medical domain as an efficient diagnostic and imaging technique. It is recognised as a well-known and highly advanced field of study. The field of ultrasound imaging is a dynamic and promising area of study that has produced significant advancements in medical imaging. These advancements include super-resolution imaging, functional/targeted contrast agents, multi-element array transducers, elastography and various other improvements [81].

In comparison to diagnostic imaging, there is far less knowledge and clinically validated applications for therapeutic ultrasound. The development of therapeutic ultrasound can be traced back to 1938 when devices were first developed to induce modest heating within the body as a means of anti-inflammatory treatment for illnesses like tendinitis or bursitis [82], [83]. The development of the field of high intensity focused ultrasound began in 1942. The application of high intensity focused ultrasound (HIFU) involves the use of continuous waves

of ultrasound at high intensity. These waves are precisely focused on a specific spot within the body, resulting in the thermal ablation of unwanted tissue. This process leads to the formation of thermal lesions [84]. The use of this particular methodology involves the potential for inadvertent negative biological effects resulting from the inaccurate alignment of the ablative beam. Nevertheless, using the technique of non-invasive tissue ablation has proven advantageous, prompting its initial application in neurosurgery to ablate abnormal tissue, and subsequently in tumour ablation [85]. During the 1960s, researchers in the field of acoustics initiated an exploration into the mechanical effects of ultrasound, specifically focusing on shock wave lithotripsy. The utilisation of short bursts of exceptionally high peak-negative pressures has become a widely accepted practice in the medical field for treating cases of kidney and bladder stones. This approach offers a non-invasive method for removing the unwanted material, hence contributing to its development as a regular treatment option [86]. The safety of mechanical and thermal ultrasound therapies experienced significant enhancements in the 1980s due to advancements in imaging and guidance systems. Specifically, the introduction of MRI-guided focused ultrasound machines expanded the application of high intensity focused ultrasound to a broader range of cancer ablation scenarios [87]. Ultrasound therapy presently integrates the thermal and mechanical components of ultrasound and is widely employed in clinics for non-invasive tissue ablation procedures. This technique is particularly valuable in cases where surgery is difficult or not possible, such as various tumour treatments. Ongoing research efforts involve a wide array of applications, ranging from the breakup of blood clots [88] to the facilitation of medication administration into tissue or across the blood-brain barrier [89]. One of the primary obstacles in the domain of ultrasound as a method for tumour ablation, similar to what has been discussed before for other cancer treatments, lies in obtaining adequate target specificity to minimise the potential for off-target ablation.

To obtain the desired outcomes, the ultrasound parameters used in ultrasound therapy must be properly modified. In therapies that employ thermal ablation through the use of high intensity focused ultrasound, longer pulses characterised by large amplitudes and high frequencies are employed. This increases the deposition of thermal energy into the tissue [90]. In the field of histotripsy, the major mechanism of tissue destruction is cavitation. This process involves the use of pulses with high amplitude (>20 MPa) and short duration (μ s).

The aforementioned process induces important forms of cavitation, yet long periods between short pulses allow for sufficient dissipation of heat, hence preventing tissue overheating [91].

A more recent development has been the use of focused ultrasound and microbubbles to deliver drugs to the brain. One of the priorities in this application is to ensure the safe and controlled behaviour of microbubbles to achieve optimal levels of permeability while minimising any potential adverse effects. The determination of safe parameters in animal research has traditionally been accomplished through empirical means, involving the systematic testing of various pressures and pulse lengths, followed by careful observation and analysis of the outcomes [74]. Hence, the selection of these parameters is not grounded in an extensive understanding of the specific bubble behaviours that need to be induced, as the exact mechanisms underlying BBB opening remain uncertain [92]. In any investigation, various characteristics necessitate consideration, such as peak negative pressure, centre frequency, pulse repetition frequency, pulse length, microbubble type, composition, and microbubble concentration [93].

In animal research, it is common to employ centre frequencies about equal to 1 MHz, accompanied by pressure amplitudes ranging from 0.2 to 1 MPa. Tone pulses, typically lasting between 2 and 10 milliseconds, are also commonly utilised. Pulse repetition frequencies often fall within the range of hertz (Hz). Several research has demonstrated the successful use of short pulses consisting of only a few cycles [94]. However, the outcomes of these studies have exhibited variability when compared to the effects of tone pulses [41], [95], [96]. Numerous contemporary in vivo investigations employ intravenous microbubble injections to attain serum concentrations in animals that closely resemble the clinical concentrations employed in imaging and therapy.

1.3.6 Ultrasound systems used in clinical trials

This section provides a concise overview of treatment approaches and introduces the equipment used in clinical settings. The subsequent sections will provide a comprehensive overview of the design aspects relative to the devices.

Numerous investigations and clinical trials have been conducted to investigate the usage of ultrasound and microbubbles to increase the BBB permeability for the purpose of drug

delivery. The first clinical trial was published that the use of ultrasound and microbubbles to enhance the permeability of the blood-brain barrier in patients with glioblastoma multiforme, a particular kind of brain tumour. Various methodologies for conducting the treatment have been examined [97]. The initial documented clinical experiment employed the use of an implantable ultrasound device system known as SonoCloud to administer plane wave ultrasound onto the brain tumours developed by Carthera [97]. The implantation of the device initially took place within the cranial bone situated above the region affected by the tumour, utilising a surgical intervention [97]–[99]. Subsequently, an ultrasonic wave was generated using extended pulses (burst length: 25,000 cycles, duration: 23.8 ms) and elevated pressure (0.8 MPa) at a frequency of 1.05 MHz. The effectiveness of this methodology in enhancing the permeability of the BBB was validated through the use of magnetic resonance imaging (MRI). Nevertheless, due to the compact size of the device (10 mm in diameter), the ultrasonic coverage area fell short of the necessary extent. The use of long pulses and high pressure may contribute to the formation of standing waves, which could inadvertently deliver drugs to unintended regions. The ongoing clinical trial of this device is currently assessing its safety and feasibility [99].

The therapy procedure involves the use of the ExAblate device, developed by Insightec Inc., which combines a hemispherical ultrasonic array with MRI guidance [38]. The patient's cranium must be securely attached to a metallic stereotactic frame, which is afterwards attached to a hemispherical array positioned on the MRI table. The array is responsible for producing focused ultrasonic waves within the patient's skull, while the MRI scanner is utilised to direct and steer the focal point towards the specific region of interest. The experimental setup involved the utilisation of a low-frequency signal with a frequency of 220 kHz, accompanied by pulses of extended duration lasting 2 milliseconds. A power ramp test was conducted to ascertain the appropriate power level and corresponding acoustic pressure for use. During the test, the power was incrementally increased by 5% until the occurrence of cavitation was found. Subsequently, the power was reduced by 50%. The permeability of the BBB was effectively enhanced, and subsequently returned to its baseline level within a 24-hour period. The therapeutic intervention yielded positive outcomes; nonetheless, the occurrence of micro-haemorrhage raises potential safety implications. Additional research

employing a comparable methodology has also demonstrated a successful augmentation of the blood-brain barrier permeability [100], [101].

Additional alternate methodologies involve the use of a transducer with a single element that is specifically focused, while there is ongoing exploration into the implementation of a neuronavigational system [102], [103]. The use of neuronavigational system is used to guide the focal point in this particular technique. Imaging techniques are employed to determine the relative positioning of the skull and the transducer, hence ensuring precise treatment delivery to the intended region.

The properties of ultrasound, including frequency, pressure, pulse length, and pulse repetition frequency, exhibit variations among different methodologies. The process of choosing the appropriate frequency and pressure is rather uncomplicated. In small animal experiments, it is common to use high frequencies (>1 MHz) due to the small size of the skull, which mitigates concerns over attenuation. An increased frequency also results in a reduced focal size, a desirable characteristic when considering a smaller brain size. Low frequencies, specifically those below 1 MHz, are preferred for use in bigger animals and people due to their ability to penetrate thick skulls more effectively [104]. The administration of drugs at higher pressure levels has been observed to enhance drug delivery; nevertheless, this practice comes with an elevated risk of inducing tissue harm [78]. According to previous research [105], the treatment's pressure threshold exhibits a drop as the frequency decreases. Pulse length is currently receiving significant attention among the parameters. All the aforementioned clinical trials employ long-pulse ultrasound, characterised by durations in the range of milliseconds. However, the use of long pulses is accompanied by specific difficulties. According to previous research, it has been established that using long pulses are significantly linked to adverse biological reactions, including bleeding and neurological harm [106]–[108]. Furthermore, the use of long pulses in brain treatment techniques has a high probability of inducing standing waves within the cranial cavity, particularly when employing low frequencies [109]. The formation of standing waves occurs from the superposition of many waves, such as therapeutic waves and their corresponding reflections. Therefore, standing waves can result in both elevated peak acoustic pressure and the possibility of additional locations with high ultrasonic pressure. Delivery or treatment of drugs can result in unintended effects on non-targeted or healthy areas, perhaps leading to secondary

bleeding [110], [111]. Furthermore, it has been observed that extended pulses have the capability to sustain the elevation of blood-brain barrier permeability for extended periods, ranging from several hours to even days, as evidenced by studies [39], [74]. This allows for a significant temporal interval during which the poisonous chemicals can permeate the brain. In recent times, there has been a growing interest in the use of short-pulse ultrasound, typically lasting for microseconds, for drug delivery. This approach has been extensively studied and demonstrated to possess the ability to provide medications safely and effectively [41], [103], [112], [113]. The use of short pulses can mitigate the risk of inducing tissue damage [114] and can also lead to a reduction in the duration of BBB disruption to around 10 minutes [41].

1.4 The transmission and reception of ultrasound wave

1.4.1 Ultrasound transducers

The piezoelectric effect serves as the underlying concept that governs the field of ultrasonic sensing and acoustics as one. A transducer is a manufactured component designed to effectively use the piezoelectric effect. A simple transducer is comprised of a segment of piezoelectric material that serves as a barrier between two electrodes. The piezo-electric material's thickness is equivalent to one-half of the wavelength corresponding to the required centre frequency [115]. The typical choice for a piezoelectric material is a polycrystalline ferroelectric ceramic compound commonly referred to as Lead Zirconate Titanate (PZT) [116], [117], a synthetic material, demonstrates a significant piezoelectric effect after undergoing the process of "poling." Poling involves subjecting the material to high temperatures while applying a substantial electric field to align the magnetic dipoles inside its structure in the direction of propagation [116], [117]. The actuation of a piezoelectric material through the application of an electric signal induces structural deformation, resulting in the generation of vibration or mechanical disturbance. The aforementioned procedure can be characterized as an electro-mechanical conversion. PZT is widely recognized for its superior electromechanical conversion factor in comparison to alternative materials [115], rendering it more effective in the conversion of electric signals into acoustic signals.

The mechanical disturbance gives rise to two waves: a forward propagating wave and a backward propagating wave. These waves have similar amplitudes but differ in polarity and

direction. The forward propagating wave is predominantly employed to sense within the system, and as a result, it becomes linked with the medium. The phenomenon of the backward propagating wave might result in internal reverberation within the component, leading to the generation of additional undesired pressure waves and elongating the transmission process. Consequently, it is customary to employ backing material in order to reduce or absorb the wave that propagates in the opposite direction [116]. According to previous research [116], commonly used backing materials, such as epoxy, exhibit a favourable acoustic impedance match with the piezo-electric material. The inclusion of a backing layer guarantees the transmission of a short, damped pulse when stimulated by an electrical impulse [115].

The propagation of the forward wave can potentially result in undesirable reflection when it is linked with a material that exhibits an important variation in acoustic impedance. The aforementioned phenomenon leads to a decrease in the effectiveness of signal transmission and a decrease in the accuracy of signal reflection. The improvement of energy transmission within the piezo-electric material and the surrounding medium can be achieved by using matching layers. Matching is frequently required for PZT due to its increased acoustic impedance in comparison to other materials such as soft tissue and water [115]. So, overall, a single-element transducer typically comprises a PZT disk together with a matching and a backing layer (Figure 1.3). The design of array transducers involves the integration of many piezo-electric elements into a unified assembly [116]. The use of many elements offers several advantages, hence resulting in an elevated level of performance or efficiency. The range of operation in both the transmit and receive modes is greater as compared to single-element transducers. The manufacturing of array transducers requires the same method as, PZT disks, backing, and matching layers applied to each element.

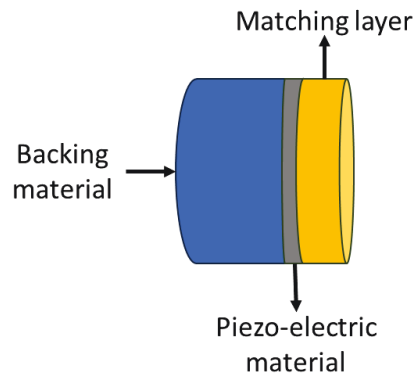


Figure 1.6. Diagram of a single-element transducer. A single-element transducer comprises a PZT disk together with a matching and a backing layer.

1.4.2 Driving/ Acquisition electronics for ultrasound transducers

An overall ultrasound system includes the generation of transmit signals, acquisition of received signals, signal processing, and delivery of information in an output format that corresponds to the requirements of the user. In a basic single-element system, the use of a waveform generator in conjunction with an RF linear power amplifier is a viable approach for the exciting single transducer. The acquisition of signals can be digitized by an oscilloscope after signal conditioning.

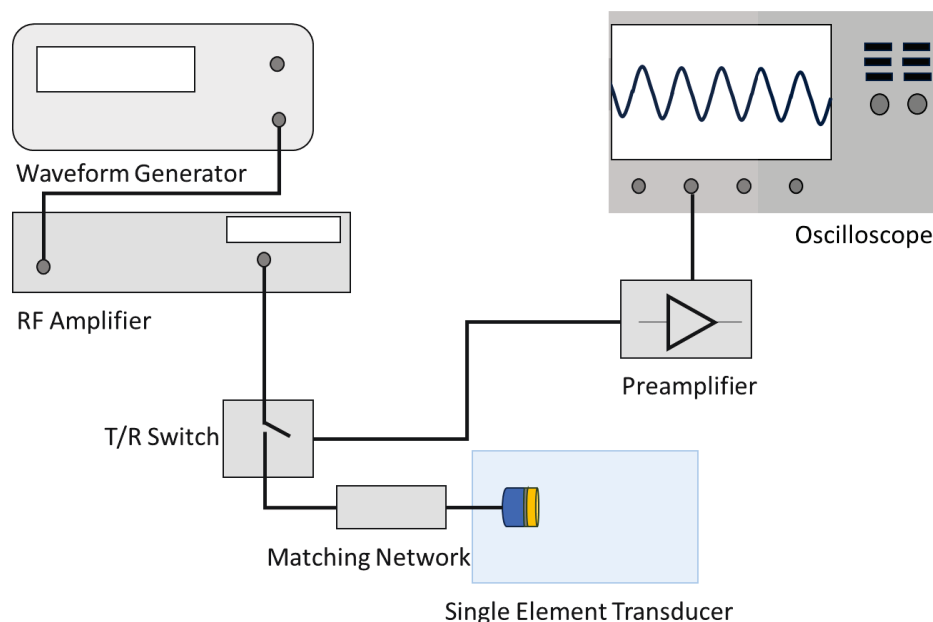


Figure 1.7. A complete single-element ultrasound driving, and acquisition system used in pulse-echo mode consists of a signal generator, amplifier, T/R switch, preamplifier, and oscilloscope.

This setup is convenient for single-element emission/reception but for multi-element systems, it is not affordable and not practical. It occupies a lot of space and is not portable. Controlling all the channels independently is difficult and per-channel cost is expensive. Therefore, it requires a multi-channel driver. Commercially available clinical drivers are capable of driving transducer arrays, but they are not user nor cheap. They often have complex systems or hardware limitations (limited working frequency range) that limit their usage. The complexity of a commercially available ultrasound imaging system designed for array transducers exceeds the complexity of a single-element system, as it contains numerous modules and subsystems. Within a clinical system, certain characteristics, including transmit sequencing and signal processing, are predetermined and contain fixed functionality. As a result of its inherent characteristics, the architecture of the system has incorporated decision-making processes that restrict its functionality to specific operational modes, hence facilitating training for medical professionals.

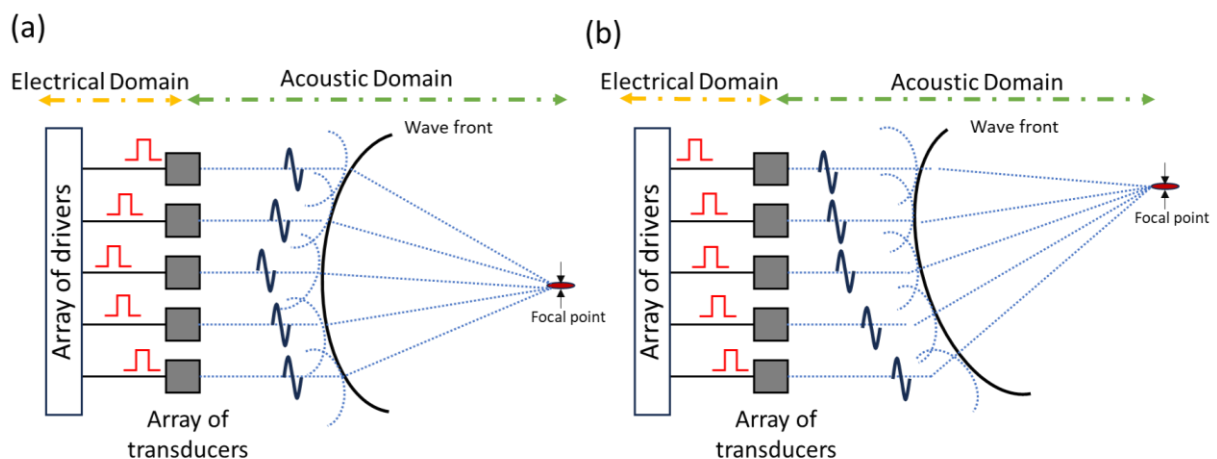


Figure 1.8. Transmit beam (a) focussing, (b) steering. The time delay associated with electrical excitations across various elements is employed to synchronize the arrival of ultrasonic waves generated by different transducers at a certain location. The method of altering the focal location is commonly referred to as steering. It should be noted that this method applies not only to linear arrays but also to other types of arrays such as dome-shaped arrays.

In a multi-channel therapeutic system, the motivation varies. In therapeutic ultrasound, transducer arrays can be used to focus and steer an ultrasound beam, allowing several localized regions in the body to be treated. Steering such an array is achieved electronically,

with a driving system that coordinates the emission from each of the array's transducers so that they constructively interfere at the target location. However, most commercially available multi-channel arrays and their drivers are designed for imaging or thermal ablation, so they are either not suitable or too expensive for other therapeutic applications, such as microbubble-based methods.

A detailed existing ultrasound driving systems will be reviewed in Chapter 1 for single-channel and Chapter 2 for multi-channel systems.

1.5 Thesis aims

This doctoral thesis aimed to design and build a multi-channel low-intensity ultrasound driver specifically for short-pulse ultrasound therapy using microbubbles. The first objective was to design and test an affordable, low-complex single-channel driver that can emit short pulses and excite microbubbles. This design was expected to introduce a new low-intensity therapeutic system which is affordable, highly scalable, and easy to replicate. The single-channel's transmitting ability was tested with electrical and acoustic tests. It has been characterized in terms of its acoustic pressure and electrical amplitude. The second objective was to incorporate this single-channel ultrasound driver into a multi-channel driver and test its performance. The multi-channel driver's acoustic performance, including waveform, focal pressure, beam profile, and steering capabilities, was tested in the free field. Then, to increase the performance of the driving system and investigate the different matching topologies, a programmable, highly dynamic matching network was developed to perform multi-frequency and multi-transducer matching from a single matching network. Overall, the research here aimed to design and build a prototype driving system that can deliver drugs and allow receive microbubble cavitations for short-pulse ultrasound therapy and investigate its performance.

1.6 References

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2 A low-cost and scalable single-channel high-voltage driver for therapeutic ultrasound transducers

2.1 Introduction

Current therapeutic ultrasound systems use single-element focussed transducers [1]–[3] or hemispherical arrays [4]–[13] to generate the required pressure at the targeted region. The single-element focussed transducer option is typically driven by a signal generator, amplifier, and matching network. As for the reception, passive cavitation detectors (PCD) [2], [3], and other single/multi-element sensors made of PVDF or PZT [4], [14]–[17] are used for the detection of acoustic pulses. Oscilloscopes or other digitization systems are used to capture the signals. However, for multi-element arrays, which can have 100s to 1,000s of elements, using individual signal generators with linear RF amplifiers per channel same as the single-element excitation approach is not feasible in terms of cost, triggering, and size of the device.

Driving electronics for multi-element arrays currently used in therapeutic systems are either designed for ultrasound imaging or High Intensity Focussed Ultrasound (HIFU) [13], [18], but are not specifically built for microbubble-based therapeutic applications. In order to be used effectively for microbubble-mediated ultrasound applications, any driving system must account for the significant number of channels, the generation of frequencies below one megahertz, and the possibility of emitting short ultrasonic pulses. Current multi-channel driver systems are either unable to meet all of these needs or are excessively costly due to the incorporation of more expensive imaging-driven features. Therefore, this thesis was aimed to build a low-cost driver circuit that can be extended to a high number of channels with individually controllable driver channels in terms of both frequency and amplitude. Before our design structure was explained, the discussion of alternative amplifier technologies and their comparison with the switched-mode approaches were addressed in this part.

Amplifiers can be divided into various classes, including class A, class B, class C, class D, class E, and class F [19]–[21], and can even be further categorised as either switching or non-switching amplifiers. The amplifier is an analogue, non-switching device that operates by amplifying a continuous signal, thereby increasing its power or voltage. This amplification process is governed by a gain parameter, which represents the ratio of the input signal to the

output signal [19], [22]. A switching amplifier class is capable of producing a switched-mode output that represents the input signal in a modulated form. The various classes of analogue amplifiers range from Class A to Class C. The amplifier classes that involve switching are commonly referred to as Classes D to F.

The most basic form of an amplifier is a Class A amplifier, which typically includes the only transistor device that is biased and operates in a linear mode, conducting in relation to the input signal. A Class A amplifier is typically characterized by its conduction angle of 360 degrees or 2π [20]. The conduction angle refers to the duration during which the output stage conducts in response to a single sinusoidal cycle input. A conduction angle of 360 degrees indicates that the output stage conducts for the entirety of the cycle. A Class A amplifier is defined by a significant quiescent current and the dissipation of power in the form of heat, regardless of the presence or absence of an input signal [23]. The dissipation of power as heat has several consequences in terms of the output stage. Firstly, it leads to an elevation in temperature, affecting the overall thermal conditions. Secondly, it imposes additional stress on the surrounding components, increasing their operational demands. Ultimately, this can lead to an expedited deterioration and failure of the system [20], [21]. In order to reduce the significant power dissipation, Class A amplifiers demand the use of heat sinks and/or the implementation of ventilation mechanisms to facilitate effective cooling. Heat sinks are characterized by their substantial weight, large size, and considerable cost [20]. Nevertheless, they are considered essential in the context of high-power Class A systems.

A Class B amplifier is designed to amplify either a single positive or negative cycle, resulting in half a period [19], [20]. Class B amplifiers are typically not used alone due to being able to cancel out half of the signal. Instead, they tend to be used in a push-pull configuration, where each device conducts based on the positive or negative half cycle that is applied. It is important to acknowledge that a Class A amplifier has the capability to operate in a push-pull configuration as well. This involves the use of two devices, where one of the input's phases is inverted. In a Class A push-pull setup, it is observed that both devices remain conducting, resulting in both angles of conduction being 360 degrees. Crossover distortion is a common problem seen in Class B (push-pull) amplifiers when the input signal falls below the bias voltage of either of the devices [23]. The phenomenon described

provides the existence of a region known as a "dead zone" centred at 0 volts, which spans a distance equivalent to double the voltage drop exhibited by the used device.

The Class AB architecture introduces a biasing technique for the push-pull transistors, enabling the amplifier to function as Class A at low signal levels. When the input is 0V the two transistors are in an electrically conductive state. However, when exposed to large input signals, the amplifier behaves similarly to Class B amplifiers. Class A/B systems offer a favourable balance between the uninterrupted conduction seen in Class A systems and the crossover distortion commonly associated with Class B designs [20]. The conduction angle of a Class A/B amplifier is contingent upon the extent to which each component conducts during its typical Class B operational phase.

Amplifier classes, such as Class D, have distinct operational characteristics. The process of modulation is employed by a Class D amplifier to turn an analogue input signal into a series of switching states. The most prevalent method of modulation is the manipulation of pulse width through comparison with a triangular carrier waveform [20]. The waveform's modulated representation is subsequently amplified through the use of a switching output stage, often employing a field-effect transistor (FET) device, which effectively determines the desired voltage level. At its most basic level, a Class D amplifier operates by alternating between two distinct voltage levels, often a ground state and another voltage, while employing a push-pull design. Most of the applications require signal conditioning such as filters to demodulate the output signal. The output transistors exhibit zero current consumption when they are not conducting, and demonstrate minimal voltage drop across the drain-source (VDS) terminals when they are conducting [19]. Therefore, Class D amplifiers exhibit a notably high level of efficiency in comparison to other analogue classes.

Class D amplifiers operate by switching at a frequency that exceeds the response time of the reconstruction filter, resulting in a time-averaged output. The inefficiency of Class D amplifiers, however, is associated with their rapid switching rates, which result in repeated high-frequency commutations and subsequent power loss. The occurrence of switching loss can be related to the continuous charging of the gate capacitance of a MOSFET at a specific frequency, denoted as C_G [19], [20]. Pulse-width modulation (PWM) has emerged as a promising technology for Class D amplifiers, as it offers notable advantages such as enhanced efficiency, compact dimensions, and increased power capacity. Consequently, these

attributes have positioned Class D amplifiers as a prospective direction for future advancements in amplifier technology. In addition to sigma-delta modulators, alternative switching amplifiers, including those employing pulse-density modulation (PDM), have gained significant acceptance in many applications. Switched-mode class D amplifiers offer cost savings and reduced heat dissipation compared to analogue amplifier technology [20]. Therefore, it is advantageous to utilise switched-mode circuits that can switch high currents at rapid speeds for piezo-electric excitation.

2.2 Aims and objectives

The primary objective of the research outlined in this chapter was to develop a low-cost and scalable single-channel high-voltage transducer driver for microbubble-based therapeutic ultrasound applications. The design aimed to address several key gaps in existing systems, which are often either too costly or too complex to meet the specific requirements of such applications. Our driver was designed to achieve the following target parameters:

1. Ultrasound Parameters:

- Centre Frequencies: Capable of operating at sub-megahertz frequencies, specifically 0.3 MHz, 0.5 MHz, and 1 MHz.
- Pulse Lengths: Generation of short pulses with lengths ranging from 1 to 20 cycles.
- Amplitude Control: Individually variable output amplitude up to 150 V peak-to-peak.
- Delay Variability: Adjustable delay to enable precise control over the emitted ultrasound waves.

2. Cost and Complexity:

- Cost Efficiency: The total cost of the individual driver circuit was aimed to be under \$12.5, significantly lower than existing commercial systems.
- Scalability: The design was intended to be easily scalable from a single-channel to a multi-channel system, suitable for high-element-count arrays.

3. Performance Metrics:

- Acoustic Pressure: Target acoustic pressure of maximum of 1 MPa peak-to-peak, measured at a distance of 15 cm from the array.
- Compatibility: Ensure seamless integration with receive circuits to detect microbubble emissions.

To achieve these goals, the circuit design was meticulously evaluated using an oscilloscope with a high-impedance probe to measure key electrical parameters. The performance of the circuit was further validated by driving an ultrasound transducer and measuring the resulting acoustic pressure field using a needle hydrophone.

Moreover, to ensure the transmit circuit's compatibility with receive circuits for detecting microbubble emissions, microbubbles were exposed to ultrasound pulses and simultaneously recorded their emissions using a transmit/receive circuit. This dual functionality is crucial for real-time monitoring and feedback in therapeutic applications.

The developed single-channel circuit demonstrated the potential to be scaled into a multi-channel driving engine, addressing the gaps in current ultrasound systems by providing a cost-effective, flexible, and high-performance solution. Further discussions on the scalability and additional applications of this technology will be presented in Chapter 3.

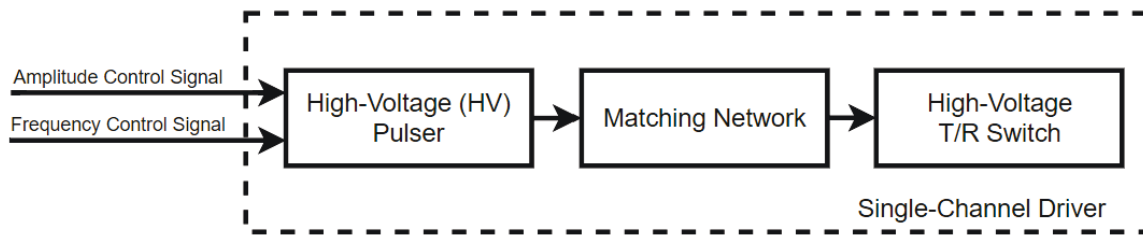


Figure 2.1. Design overview of the proposed single-channel driver. A single-channel driver system contains a high-voltage pulser (HV) design, a matching network, and a high-voltage switch.

2.3 Materials and methods

2.3.1 Single-Channel Driver Design

a) High-voltage pulser design

The single-channel driving circuit was designed to generate high-voltage square pulses that would be filtered through a matching network to generate sinusoidal pulses out of a transducer, and a high-voltage T/R switch allowing low-voltage acoustic signal reception (Figure 2.1). The driving circuit was designed with two digital input signals (ranging from 0 to 3.3 V) so that the user could adjust its amplitude, centre frequency, pulse length, and phase. The first digital input – the amplitude control signal – dictated the amplitude of the

square pulse. The second digital input – the frequency control signal – dictated the centre frequency, pulse length, and phase of the square pulse.

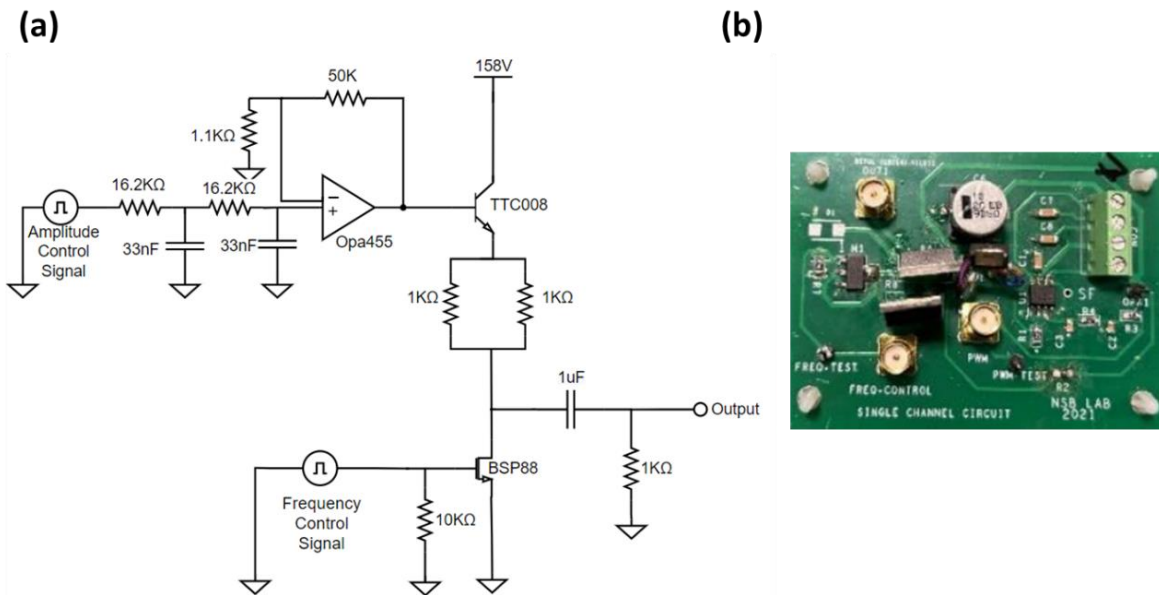


Figure 2.2. Single-channel high-voltage square wave pulse generator (HV Pulser). (a) A digital control unit (not shown here) dictates the amplitude via the amplitude control signal input (0-3.3 V) and the centre frequency, pulse length, and phase via the frequency control signal (0-3.3 V). (b) A populated printed-circuit board (PCB) of the design.

The magnitude of the square pulse was determined by the duty cycle of the digital amplitude control signal the pulse-width modulation (PWM) technique. The digital input signal in the kilohertz range was filtered using a simple second-order low-pass filter (RC) with a cut-off frequency of approximately 300 Hz. This removed the high-frequency components of the digital amplitude control signal input, producing a direct current (DC) signal within the range of 0 to 3.3 V. The voltage level was set within this range by setting the duty cycle of the digital amplitude control signal. Duty cycles between 5% and 99%, would produce DC signals between 0.165 V and 3.267 V, respectively. In this particular instance, when a digital signal with a duty cycle of 5% was applied, the output of the low-pass filter yielded a direct current (DC) signal 0.165 V. The DC signal was then amplified using a High-Voltage/ High Output Current operational amplifier [24] (OPA455; Texas Instruments, Dallas, TX, USA) in a non-inverting amplifier configuration, with a gain of 46. The OPA455 is an operational amplifier (op amp) characterised by a high voltage rating of 155 V and a high current drive capability of 45 mA. The device under consideration exhibits unity-gain stability and has a gain-

bandwidth product of 6.5 MHz. The OPA455, a high-voltage operational amplifier, has high precision and a broad output swing range. Furthermore, it does not suffer from the phase inversion issues sometimes encountered in comparable operational amplifiers. To ensure the safety and stability of the circuit connected to our PWM-controllable amplified voltage output, a bipolar-junction transistor (BJT) model TTC008 [25] manufactured by Toshiba Semiconductor in Japan was employed. This BJT was configured in a voltage follower/buffer mode, serving as an intermediary component between the amplifier output and the switch. Its purpose was to protect the circuit and deliver an adequate current.

The digital frequency control signal was connected to a metal-oxide-semiconductor field-effect transistor (MOSFET) model BSP88 [26], manufactured by Infineon Technologies AG in Munich, Germany. This particular MOSFET was used in switch mode. When the digital signal reached a high voltage level of 3.3 volts, the MOSFET's gate terminal biased with a voltage greater than the threshold voltage (V_{th}) led the device to enter an active state causing a flow of electric current between its drain and source terminals. The MOSFET switch was in the OFF state when the digital signal was at a low voltage of 0 V. This led to the occurrence of current flow through the load, which, in our specific application, was the PZT transducer. Consequently, there was no current flow via the drain to the source terminal of the PZT transducer when the device was in the cut-off region. Therefore, when the switch is in the ON state, the MOSFET operates in saturation mode, resulting in a low signal (0 V) being received by the transducer. In contrast, when the switch is in the OFF state, the Metal-Oxide-Semiconductor Field-Effect Transistor (MOSFET) enters the cut-off mode. Consequently, the transducer is subjected to a high signal with an amplitude ranging from 0 to 150 V. This amplitude is set by the aforementioned amplitude control signal. In this configuration, the MOSFET switch works as an inverter. When 10 pulses from the frequency control signal at an amplitude of 150 V (99 % duty cycle) were sent, the transducer received a 0-150 V signal in 10 cycles but there was a 150 V DC offset. DC offset caused by the OFF condition of the MOSFET switch was removed by using a DC blocking capacitor value of $1\mu\text{F}$ in series.

b) Low-pass filter/ matching network design

The square wave pulses with high voltage, which are produced by the MOSFET switch, undergo filtration before they're transmitted to the ultrasound transducer. The filter transformed the square pulse output into a sinusoidal waveform. The filtering mechanism

was comprised of an inductor connected in series with each channel. The filter effectively attenuated high-frequency harmonics included in the required signal, enabling the transmission of a high-voltage sinusoidal wave with the desired frequency and power to the piezoelectric elements. Additionally, it served as a matching network, facilitating the connection between the amplifier's output and the transducer that was linked to it. An inductor with an inductance value of 120 μH was employed to achieve a desired frequency of 0.5 MHz. The HV-pulser and low-pass filter/matching network were designed in separate PCB allowing for adaptability to other frequencies. It is possible to modify the components in order to accommodate different frequencies.

c) High-voltage protection transmit/receive (T/R) switch

A PCB by using four integrated chips MD0101 [27] (Microchip, Arizona, USA) was designed, which is a protective device designed to limit current in high-voltage systems, with four channels. The purpose of this device is to protect a low-noise receiver against high-voltage transmit pulses in ultrasound applications. It is usually known as a transmit-and-receive (T/R) switch. Every channel is equipped with three terminals, namely TX, RX, and RGND. The terminals of the analogue switch are denoted as TX and RX. The RX module incorporates clamping diodes connected to RGND to safeguard the receiver from potential damage caused by excessive voltage levels. The antiparallel diodes will limit the output voltages to approximately $\pm 0.6\text{V}$, clamping them to RGND. When the MD0101 is in the OFF state, it has the ability to function under a voltage of up to $\pm 100\text{V}$ across its terminals. The reason behind using this switch is its cost and not requiring external supplies or control signals to turn on. It also has low on-resistance around 15Ω . When the voltage across Terminals TX and RX exceeds 2V, the switch transitions into Transmit mode, which blocks the transmission of high-voltage pulses to the receiver.

2.3.2 Electrical characterization

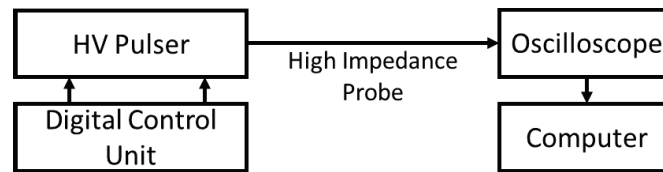


Figure 2.3. Electrical characterization experimental setup. The experimental setup was used to test the performance of the high-voltage pulser. The pulser was tested by using a high-impedance probe for different frequencies, number of cycles, and amplitude.

First, the electrical responses of the individual drivers were tested without connecting the transducer as a load to understand the behaviour of the driver and measure the linearity of the controllable amplitude control output between channels. Two function generators (33500B; Keysight, Santa Rosa, CA, USA) were used to generate the digital input signals. Various amplitude control signals (duty cycle: 5% to 99%, frequency: 10 kHz) and frequency control signals (20 cycles, 0.1-1MHz) were generated and connected to the high-voltage driver circuit. The output of the single-channel driver circuit was recorded using an oscilloscope (MDO3000 Mixed Domain Oscilloscope, Tektronix Inc., Beaverton, OR, USA) with a high-impedance probe. The electrical performance of a single-channel high-voltage driver was evaluated for various frequencies, pressures, and number of pulses.

2.3.3 Acoustic characterization

The performance of the single-channel driver in conjunction with a transducer (loaded condition) was tested (Figure 2.4). The experiments were performed in a tank which was filled with degassed and deionized water. A custom-made 0.5-MHz and 0.3MHz PZT transducers were used for emission. The first PZT which was one of the elements from the hemispherical array was excited with a 1-cycle pulse at 0.5 MHz by our single-channel driver both with and without a low-pass filter (Figure 2.4(b)). The second custom-made PZT was excited with 10-cycle pulses at 0.3MHz (Figure 2.4(c)). Finally, the driver was tested with a commercial 1 MHz transducer (Olympus, Tokyo, Japan) to be able to see its performance acoustically for different frequency ranges (Figure 2.4(a)). The amplitude of the signal was varied using a duty cycle between 5% and 99% to evaluate the pressure variation over different transducers. The transmitted ultrasound pulses were captured by a commercial 1-mm-in-diameter needle hydrophone (Precision Acoustics, Dorchester, UK) located based on

the individual transducer's focal point fixed on a 3D-positioning system. The received signals were then digitized by a GaGe digitizer (Octave 14, Dynamic Signals, San Bruno, CA, USA), before being stored on a computer. The acoustic performance of a single-channel high-voltage driver was evaluated for various frequencies, pressures, and number of pulses.

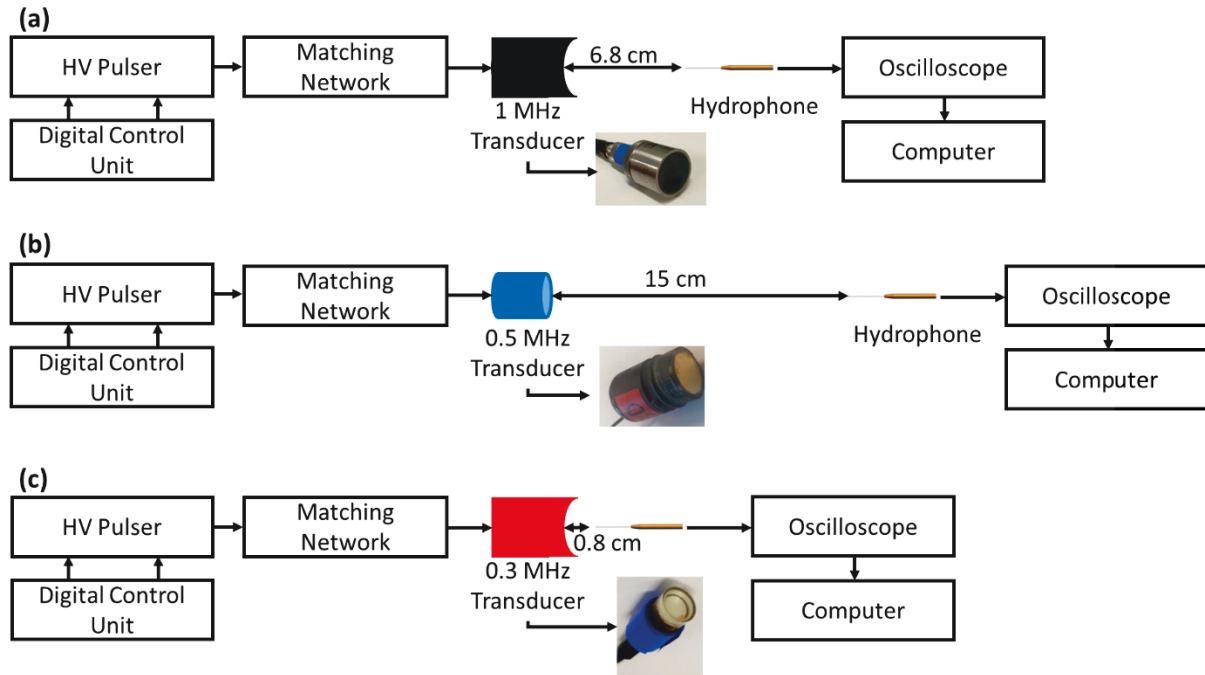


Figure 2.4. Acoustic performance of single-channel driver. The experimental setup was used to evaluate the single-channel driver's performance with different transducers for frequencies at (a) 1 MHz, (b) 0.5 MHz, and (c) 0.3 MHz. Acoustic signals were captured by a 1mm needle hydrophone, digitized with an oscilloscope, and stored on a computer.

2.3.4 Microbubble excitation and reception

The microbubbles used in this study were produced in-house, using a process that has been previously published [28]–[30]. In short, to make microbubbles, a mixture of dipalmitoyl phosphatidylcholine (DPPC-82%), dipalmitoyl phosphatidylethanolamine–PEG5000 (DPPE–PEG5000-10%) and dipalmitoyl phosphatidic acid (DPPA-8%), was initially prepared. This mixture was then diluted with saline and glycerol. Subsequently, perfluoro butane was introduced into the mixture, and to create actual bubbles vials were agitated for approximately 45 seconds in the vial mix shaker (Synergy Electronics, Scottsdale, AZ, USA). The microbubble formulation was chosen based on the acoustic resemblance between commercially available clinically approved Definity microbubble formulation [31]–[36]. The

microbubbles were removed from the vial using a 20G syringe needle, with an additional needle serving as a vent hole to facilitate pressure equalisation within the vial. Subsequently, the microbubbles were diluted in a solution of 0.9% phosphate buffer saline (PBS). A thorough analysis of the microbubble population were conducted by employing optical microscopy and image processing methods [37]. The mean microbubble radius was $0.70\ \mu\text{m}$ with some variation (standard deviation of $0.4\ \mu\text{m}$) and a range of sizes from $0.24\ \mu\text{m}$ to $3.97\ \mu\text{m}$ [28], [29], [38].

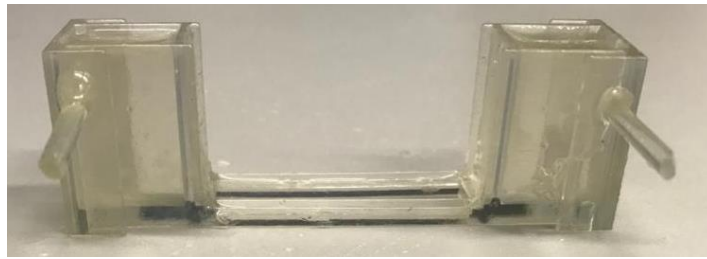


Figure 2.5. 3D printed wall-less channel frame [39].

Polyacrylamide offers ideal features for ultrasound experiments owing to its great optical and acoustic transparency, as well as its adjustable mechanical properties that enable the creation of soft gels with Young's modulus comparable to that of soft tissues [39], [40]. A polyacrylamide gel was synthesised by combining powdered acrylamide monomer with powdered N, N'-methylene bis-acrylamide, which served as a crosslinking agent. The solutions that had been degassed were subsequently combined at ambient temperature with $0.1\ \text{g}$ per $100\ \text{ml}$ of Ammonium Persulphate and $100\ \mu\text{l}$ per $100\ \text{ml}$ of TEMED. The resulting mixture was promptly put into the 3D-printed channel frame to create the $100\text{-}\mu\text{m}$ -in-diameter channels to mimic blood vessels. Wire templating method was used [39], [41]. The gel was allowed to solidify for 1 hour. After the gel had solidified, the wire was extracted, and a diluted solution of microbubbles produced in-house was injected into the channel with a hydrostatic pressure applied for the flow of microbubbles. The hydrogel channel had a Young modulus of elasticity of $3.24 \pm 0.58\ \text{kPa}$ which is closer to the tissue stiffness [40].

The experimental procedure was conducted using water that had been degassed and deionized (Figure 2.6). First, a hydrogel channel with a diameter of $100\ \mu\text{m}$ positioned within the water tank, then a 1MHz transducer (Olympus, Tokyo, Japan) was positioned in a perpendicular orientation to the channel, maintaining a distance of approximately $68\ \text{mm}$. This guaranteed that the focal point of the Olympus transducer was aligned with a specific

region within the channel. The 1MHz transducer was excited by the designed single-channel driver controlled by two function generators (33500B; Keysight, Santa Rosa, CA, USA). The excitation frequency utilised in the experiment was 1 MHz, while the pulse length was set to 3 cycles. The transducer was stimulated in order to produce ultrasonic waves with a peak-negative pressure (PNP) around 0.5 MPa. Microbubble cavitation signals were collected by a 1MHz Olympus transducer received by using the high-voltage protection T/R switch. The collected signals were subsequently digitised using a Gauge digitizer (Octave 14, Dynamic Signals, San Bruno, CA, USA) and data was saved in a computer. Two sets of experiments were conducted. The initial group featured as a control group in which a solution of saline was being circulated through the channel. The second group used a mixture of microbubbles and saline solution, to ensure clinical relevance specifically a diluted microbubble vial mixed with saline at a ratio of 1:100. Five sonications were conducted on each set. For triggering the whole spectrum of acoustic cavitation dynamics, range of pressures from 25kPa to 1MPa were tested for therapeutically relevant frequency range for brain therapy (<1MHz).

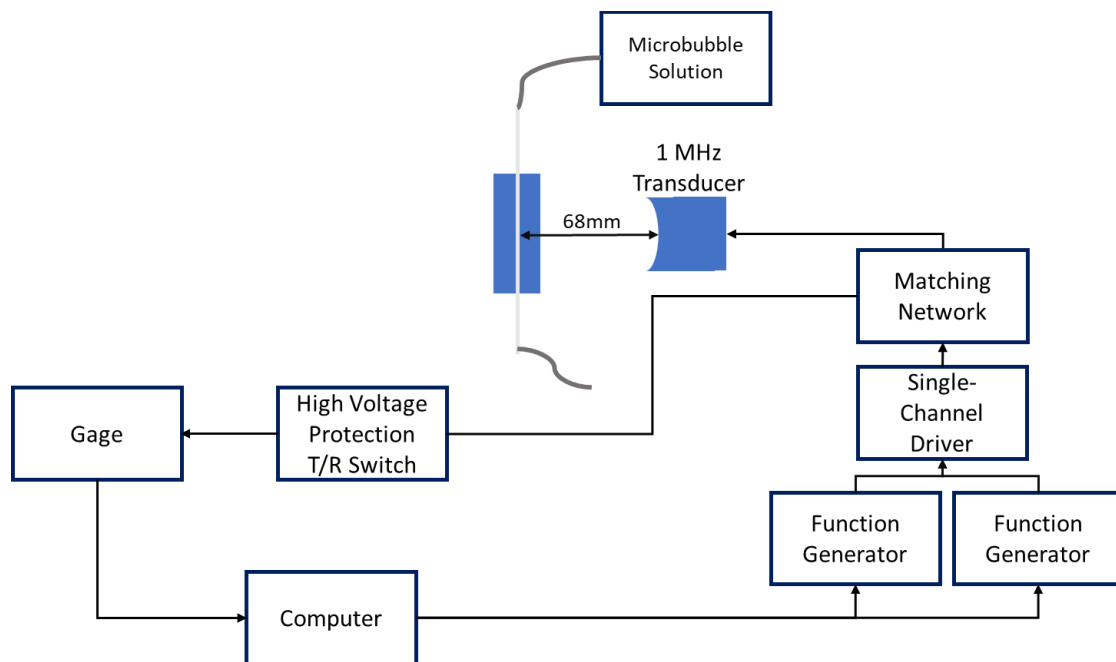


Figure 2.6. Experimental setup for microbubble excitation and reception of cavitation signal. Microbubbles were flowing inside a $100\ \mu\text{m}$ diameter channel and a 1 MHz focussed transducer was excited by a single channel driver which was controlled by 2 function generators connected to a computer. The cavitation signals were collected by transducer using a high-voltage protection switch and digitized before being recorded by a computer.

2.4 Results

2.4.1 Electrical characterization

First, the electrical responses of the high-voltage pulser were tested without connecting the transducer as a load to understand the behaviour of the driver (e.g. loading effect) and measure the linearity of the controllable amplitude control output with the PWM signal.

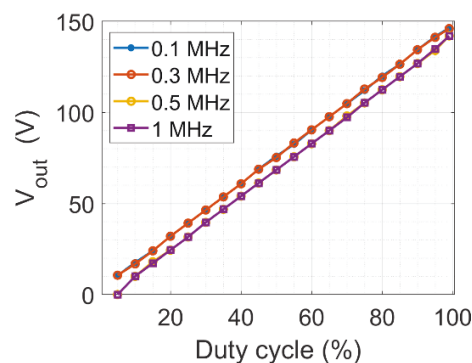


Figure 2.7. Electrical behaviour testing for duty cycle vs output amplitude. Single-channel driver output was measured with a high-impedance probe when the low-pass filter was not connected. The duty cycle varied from 5 % to 95 % with the increment of 5 and the final output measured at 99 %.

Two function generators (33500B; Keysight, Santa Rosa, CA, USA) were used to generate the digital input signals. Various amplitude control signals (duty cycle: 5% to 99%, frequency: 10 kHz) and frequency control signals (20 cycles, 0.1-1 MHz) were generated and fed to the high-voltage driver circuit. The output of the circuit was recorded using an oscilloscope (MDO3000 Mixed Domain Oscilloscope, Tektronix Inc., Beaverton, OR, USA) with a high impedance probe (Figure 2.3). The single-channel driver produced unipolar pulses with very low ripple for short duration. Due to our application requirements (short-pulse lengths), there was no need to install bulky and costly heat sinks. Despite the lack of heat sinks, there was not any significant temperature change. With the consideration of the high storage time of the TTC008 BJT ($3.3 \mu\text{s}$) and the time needed for second-order low-pass filters, the operation frequency range of our design was kept between 0-1MHz which was perfectly fitting in our application. The HV-pulser can produce pulses higher than 1MHz but there may be an overshoot problem.

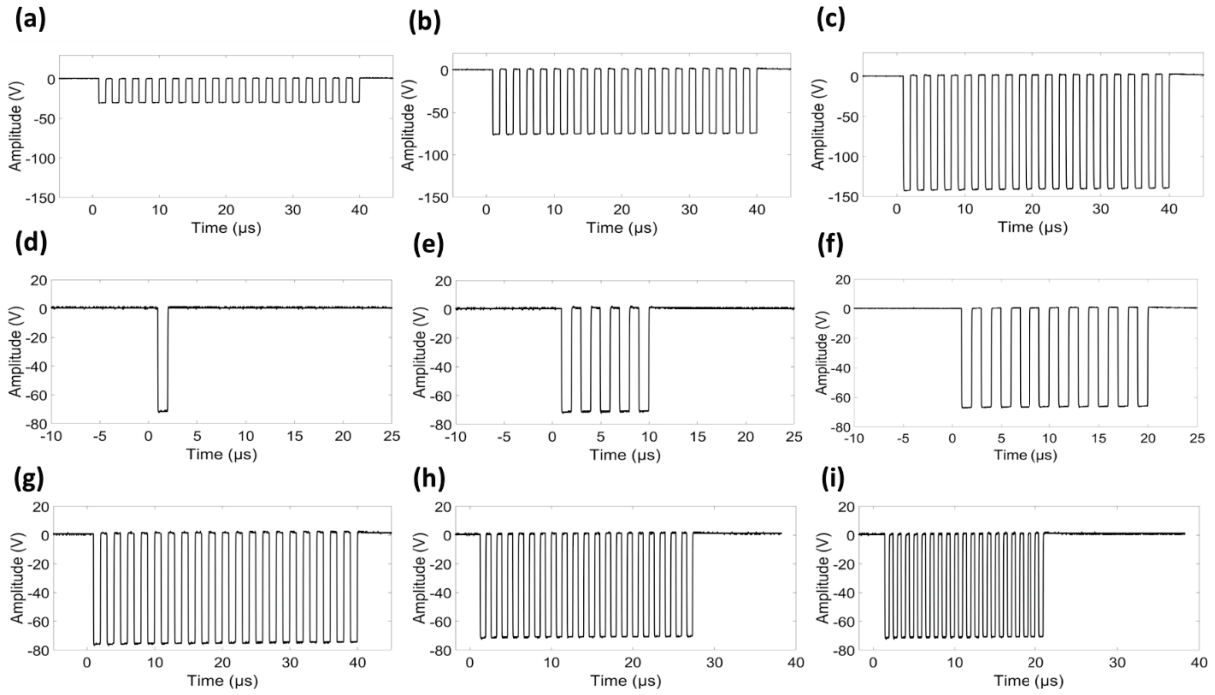


Figure 2.8. Electrical behaviour testing for different settings. Waveforms produced from the single-channel driver for different settings: amplitudes of 40 V (a), 75 V (b), 145 V (c); number of cycles of 1 (d), 5 (e), 10 (f); frequencies of 0.5 MHz (g), 0.75MHz (h), 1MHz (i).

2.4.2 Acoustic characterization

The performance of the driver circuit in conjunction with a transducer (loaded condition) was then tested (Figure 2.4(a)). The experiments were performed in a tank which was filled with deionized water. A custom-made 0.5-MHz PZT flat transducer, a custom-made 0.3 MHz focussed PZT transducer, and a commercially available 1 MHz transducer were used for emissions. The first PZT was excited with 3-cycle pulses at 0.5 MHz by our single-channel driver both with and without a low-pass filter and the transmitted ultrasound pulses travelled 15 cm away from the transducer and were captured by a commercial 1-mm-in-diameter needle hydrophone (Precision Acoustics, Dorchester, UK) fixed on a 3D-positioning system. Time and frequency domain of the transmitted wave digitized by the oscilloscope previously mentioned, before being stored on a computer, and then plotted in MATLAB.

The same experimental setup was applied for other transducers (0.3 MHz and 1MHz), but they were positioned at their focal point in the water tank with respect to the hydrophone (Figure 2.4). The amplitude of the output pressure was varied using a duty cycle between 5% and 95% for 0.3 MHz and 0.5MHz transducer, a duty cycle between 5% and 70% for 1 MHz transducer to evaluate the pressure response against duty-cycle (Figure 2.10(d), (e), (f)) and

their corresponding waveform in time domain at the maximum duty cycle applied plotted in MATLAB (Figure 2.10(a), (b), (c)). The output of the 1 MHz transducer was mostly linear, but the increase rate with the duty cycle slowly dropped after >800 kPa.

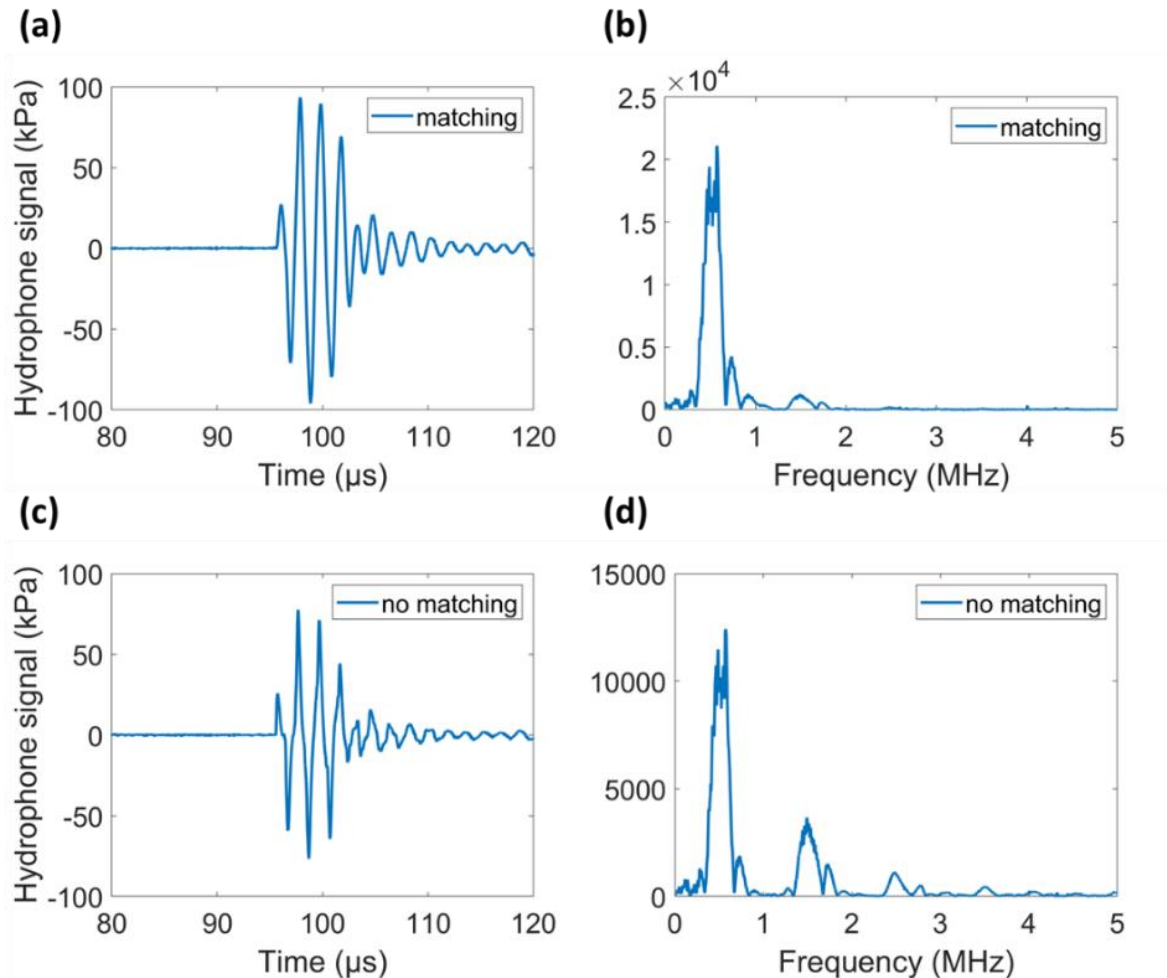


Figure 2.9. Acoustic testing to observe the effect of the matching on the output signal.

Waveforms were generated by a single PZT transducer which was excited with 3 cycles, 0.5 MHz, and 95% duty cycle (approximately 150 Vpp) by a single-channel driver. Acoustic emissions from the transducer were captured by a 1-mm needle hydrophone. The captured waveforms time-domain (a), (c) and frequency domain (b), (d) without a low-pass filter and (c), (d) with a low-pass filter connected (a), (b).

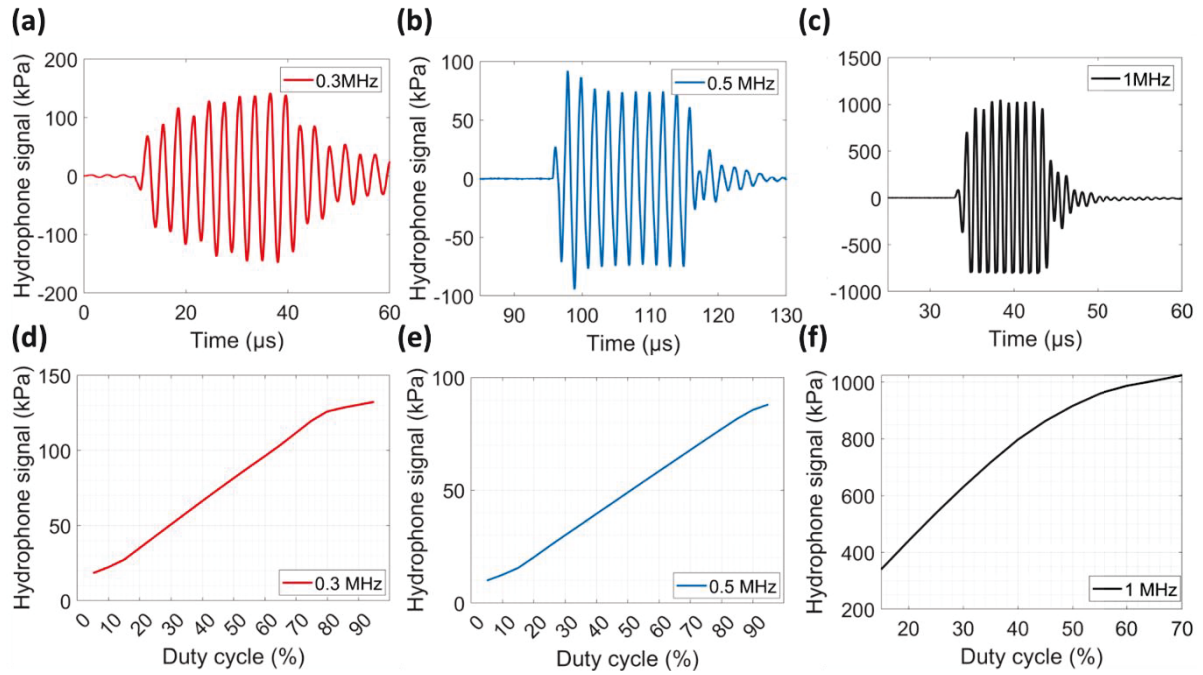


Figure 2.10. Acoustic testing for evaluating the performance of the single-channel driver with different transducers and their corresponding pressure vs duty cycle responses. Waveforms were generated by three different transducers (0.3 MHz, 0.5 MHz, and 1 MHz) which were excited with 10 cycles. Acoustic emissions from the transducer were captured by a 1-mm needle hydrophone. The captured waveforms in the time domain at 95 % duty cycle excitation (a, b) and 70 % duty cycle excitation (c). Duty cycle vs pressure output plotted for 0.3 MHz (d), 0.5 MHz(e), and 1 MHz (f).

2.4.3 Microbubble excitation and simultaneous reception of microbubbles

The piezoelectric ceramic material lead zirconate titanate (PZT) was capable of detecting acoustic emissions produced by microbubbles when subjected to sonication using 3-cycle pulses at a frequency of 1 MHz and pressure of 0.5 MPa. Even though there was no signal conditioning for the PZT transducer, it was able to receive bubble signals. High-voltage protection T/R switch allowed simultaneous reception of microbubble signals without actively switching from transmit to receive. Since PZT/PVDF stacked transducer was used [16], PVDF could have been used for reception of broadband microbubble signal from the same excitation location [42]. But T/R switch only allows us to switch between transmit and receive from the same element, so PZT was used for emitting and reception. The received signal exhibited a waveform with a duration exceeding three complete cycles, mostly attributed to the presence of the ringing phenomenon induced by the PZT.

In terms of frequency response, it was determined that the signals detected by the 1 MHz focussed piezoelectric transducer were predominantly centred around its basic resonant frequency of 1 MHz (Figure 2.11(b)). However, the microbubble signal still exhibited some subharmonics and high-order harmonics.

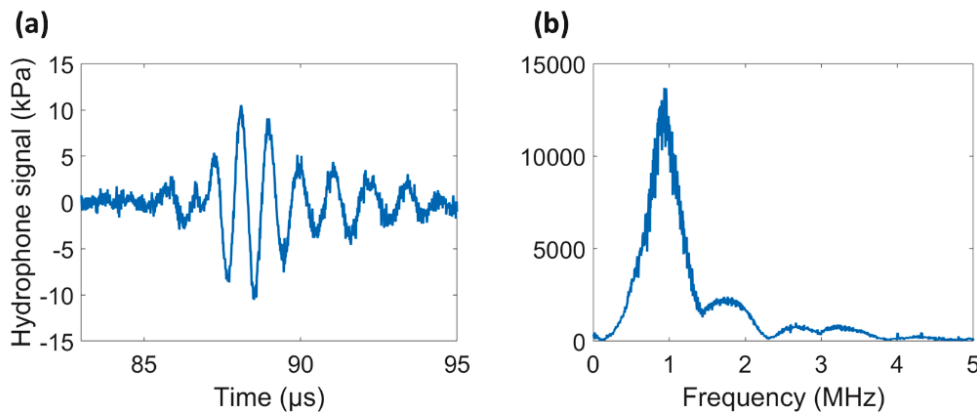


Figure 2.11. Received microbubble signals from the 1 MHz focussed PZT transducer. 1 MHz focussed transducer was excited with 5 cycles at 0.5MPa and positioned 6.8cm away from the wall-less channel. Received microbubble signals in the time domain (a), and in the frequency domain (b).

2.5 Discussion

2.5.1 Single-channel driver

Our single-channel driver can produce pulses with a maximum amplitude of approximately 150V. 0.5 MHz custom-made PZT transducer, with a low-pass filter network connected can produce an average pressure of 80kPa at the maximum excitation amplitude. Due to the required settling time for low-pass filters and storage time for TTC008 BJT (3.3 μs), in each duty cycle change frequency signal is sent at least 1 second after the amplitude signals. The optimal working frequency range of the driver is kept between 0-1MHz. Additionally, chosen MOSFETs are driven with function generators directly and do not require gate drivers. For higher frequencies greater than 1MHz, faster MOSFET switches could be used with gate drivers. The chosen MOSFET was fast enough for BBB opening applications and working with CMOS-logic level input (0-3.3V) directly which is important for affordability. The filter design could also be optimized to increase the pressure amplitude while still removing unwanted harmonics. Finally, the output resistance of the driver is chosen based on the impedance of the current transducers from the array, but it could be lowered for other devices.

2.5.2 Electrical characterization

The single-channel driver was capable of producing square-wave unipolar pulses for a short duration. The high-impedance probe measurement proves its performance on different frequencies, amplitudes, and number of cycles (Figure 2.8). The circuit was not tested in terms of the waveform when the transducer connected, it was only being tested with the probe itself. Therefore, waveforms will be different for loaded conditions. Also, it can be seen that from the duty cycle vs amplitude graph (Figure 2.7), the output voltage slightly decreases when the frequency increases, but it still behaves linearly across the entire frequency range.

2.5.3 Acoustic characterization

The performance of the driver circuit in conjunction with different transducers under loaded conditions was experimentally examined, as illustrated in Figure 2.4. The tests were conducted within a water-filled tank, using a selection of transducers for emissions. Specifically, a custom-made 0.5-MHz PZT flat transducer, a custom-made 0.3-MHz focused PZT transducer, and a commercially available 1-MHz transducer were employed.

First, the 0.5 MHz PZT transducer was excited with 3-cycle pulses using our single-channel driver, both with and without a low-pass filter. The resulting ultrasound pulses, which travelled a distance of 15 cm away from the transducer, were captured by a commercial 1-mm-in-diameter needle hydrophone. The peak-to-peak pressure of the ultrasound pulses was measured to be 75 kPa with the low-pass filter and 70 kPa without it. The time and frequency domain characteristics of the transmitted waves were digitized by the oscilloscope, sampled at a rate of 100 MS/s, stored on a computer, and subsequently analysed and plotted using MATLAB.

The experimental setup was replicated for the 0.3 MHz and 1 MHz transducers, positioned at their focal points. The 0.3 MHz focused PZT transducer, excited similarly, produced peak-to-peak pressures of 110 kPa and 95 kPa with and without the filter, respectively. The 1 MHz transducer yielded peak-to-peak pressures of 1 MPa and 0.95 MPa with and without the filter. The frequency spectra showed fundamental frequencies at 0.3 MHz, 0.5 MHz, and 1 MHz

The obtained results demonstrate the adaptability and efficacy of the driver circuit in conjunction with various transducers across different frequencies. The systematic variation of the duty cycle from 10% to 50% allowed for a comprehensive analysis of pressure response characteristics, revealing a linear increase in peak-to-peak pressure with a correlation coefficient of 0.98 for all 3 different frequencies. This shed light on the impact of the duty cycle on transducer performance. The comparison between transducers operating at different frequencies further contributes to our understanding of their behaviour under varying experimental conditions.

2.5.4 Microbubble excitation and reception

Our single-channel driver demonstrated its capability on microbubble excitation (Figure 2.11) and the T/R switch allowed us to capture microbubble signals without the requirement of active T/R switching which requires external controlling and external supplies. We should note that we used a focussed commercial PZT transducer to excite the microbubbles and receive from the same transducer. Due to its narrow bandwidth, the captured signals would be distorted/filtered. The actual broadband microbubble signal can be detected with more sensitive sensors such as PVDF transducers or needle hydrophones [15], [43]–[46]. Additionally, because of the low-pressure output of array elements around 80kPa, we could not use the 0.5 MHz PZT transducer to excite microbubbles. With a focussed transducer, the single channel driver can potentially be used for microbubble excitation in vivo experiments.

2.5.5 Integrating into a multi-channel driver

The design of a single-channel driver was specifically developed to construct a multi-channel driver, capable of supporting a varying range of channel numbers ranging from tens to thousands. The objective was to achieve an efficient design method suitable for driving large-scale arrays. The design kept it as simple as possible to lower the design cost without sacrificing the flexibility. The HV-pulser and low-pass filter/matching network were designed in separate PCB allowing for adaptability to other frequencies. It is possible to modify the components in order to accommodate different frequencies. The use of a high-voltage pulser design in multi-channel array drivers could lower the price of electronics and can produce enough pressure at short pulses to be able to deliver drugs into the brain. Recent research shows that rapid short pulse (RaSP) requires approximately 0.4MPa pressure to disrupt the BBB temporarily while enabling drug delivery [1], [33], [47]. Our single-channel driver can be

produced with the existing PZT transducers 80kPa at the maximum applied duty cycle. With a better matching network, this can be improved. The required pressure could be produced with a 5-channel driver without considering the skull attenuation. For 0.5 MHz around 20 % to 30 % [48]–[50] of the pressure can pass through the human skull and reach the targeted area, therefore around 25-30 channel drivers can produce enough pressure for brain drug delivery.

2.5.6 Limitations

The circuit was not tested in terms of the waveform when the transducer connected, it was only tested with the probe itself. Therefore, waveforms will be different for loaded conditions. Also, the output resistance of the driver chosen is based on the existing array transducers' impedance, therefore it requires an optimization to use with other transducers. But since the driver is producing square-wave pulses an impedance matching is essential to remove the unwanted harmonics. Additionally, because of the low-pressure output of array elements around 80kPa, we could not use the 0.5 MHz PZT transducer to excite microbubbles instead we used a commercially available PZT transducer.

2.6 Conclusion

Ultrasound-mediated therapies necessitate specific design specifications to enhance treatment efficacy and safety, including a large number of channels, sub-megahertz frequency outputs, and potentially short pulses. Current ultrasound systems fail to meet all these requirements or are prohibitively expensive and complex to use.

Our research introduces a novel, low-complexity, and affordable single-channel driver designed to drive arrays with high element counts. The robust performance of this driver was demonstrated through comprehensive acoustic and electrical tests. Key contributions of our work include:

1. **Cost-Effective and Simplified Design:** Our single-channel driver offers a cost-effective and simplified alternative to existing systems, making advanced ultrasound therapy more accessible.
2. **Frequency Versatility:** The driver efficiently operates with transducers at different frequencies (tested with 0.3 MHz, 0.5 MHz, and 1 MHz), meeting the sub-megahertz requirement crucial for many therapeutic applications.

3. Short Pulse Generation: The ability to generate short pulses, as demonstrated in our tests, aligns with the specifications needed for precise and safe ultrasound-mediated treatments.

4. High Element Count Compatibility: Our system is designed to drive arrays with high element counts, essential for advanced therapeutic applications that require fine control and high spatial resolution.

By integrating rapid prototyping of transducers, as referenced in [12], our system presents a potential low-cost treatment device for brain therapy. This research provides a significant advancement in ultrasound technology, offering a practical and scalable solution that bridges the gap between performance, cost, and complexity in current therapeutic ultrasound systems.

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3 The design and optimization of a multi-channel low-intensity therapeutic ultrasound driver

3.1 Introduction

Therapeutic ultrasound arrays have the ability to the shape of a focused beam [1], [2] and correct any distortions that may occur as ultrasound waves penetrate different materials, including the skull and rib cages. These capabilities are attained by exciting each transducer element with relative time differences, specified by a multi-channel driver system. This ensures that the pulses emitted from each of the many transducers arrive at the target location despite having travelled different paths.

The cost of producing therapeutic ultrasound arrays has experienced a significant decrease over time, primarily due to the advent of fast 3D-prototyping processes [3], [4]. However, it is important to note that the cost of multi-channel driving systems has remained relatively high. Moreover, it is worth noting that a significant number of the driving systems used in conjunction with transducer arrays have been primarily developed for alternative purposes, such as ultrasound imaging or high-intensity focused ultrasound (HIFU). These applications have distinct sets of requirements that differ from those of microbubble-based therapeutic ultrasound applications, which are currently experiencing an increase in use [3], [5]–[7].

The majority of multi-channel ultrasound driving systems that have been created for HIFU arrays [8]–[12] are specifically built to function in continuous mode. This is done to deliver an adequate amount of energy to effectively ablate tissue. However, therapeutic uses, including the delivery of drugs across the blood-brain barrier, can be achieved by applying short ultrasonic pulses consisting of 1-10 cycles [13], [14]. Existing HIFU systems cannot fulfil these objectives efficiently due to their design focus on continuous-mode operation, which unnecessarily increases the complexity and cost of the driving electronics for therapeutic applications. By eliminating the need for continuous-mode operation, the affordability of ultrasound array technologies might be significantly improved, resulting in a major decrease in the cost of driving electronics. To achieve a more precise ultrasound focus and improved steerability, therapeutic ultrasound arrays require a greater number of elements, typically exceeding 256. The feasibility of implementing this technique would be enhanced by the availability of lower-cost circuits.

Multiple research teams have designed and implemented multi-channel ultrasound systems that are compatible with array transducers, including SARUS [15], UARP [16], and ULA-OP [17], [18]. The Ultrasound Advanced Open Platform (ULA-OP) and its most recent iteration, ULA-OP 256 [19], [20], a portable array platform, has been created by the University of Florence [17], [18], [21]. This platform is based on a sigma-delta type of transmitter as described in [22]. The platform is equipped with 64 channels, offering a sampling rate of 50 MSPS and a resolution of 12 bits. It allows users to access pre-beamformed or raw RF data. Consequently, the approach has gained significant popularity and is widely utilised in Doppler [23]–[25] and nonlinear imaging [26]. The FPGA generates a sigma-delta bitstream for each channel, which is subsequently filtered and amplified at the front end to produce a high-voltage output. One limitation of the system, as noted in reference [17], is the excitation voltage, which is restricted to a maximum of 24 Vpp. While this is sufficient for many ultrasound imaging applications, this is too low for therapeutic ultrasound. This constraint is likely attributed to the necessity of linear power amplifiers that are needed to amplify signals to high voltage levels. In the system, the sigma-delta technique is employed as a substitute for a high-speed digital-to-analogue converter (DAC), as demonstrated in their prior single-channel platform [24], [26], and [27]. In their publication [17], the authors acknowledge the possible constraint of a deficient output voltage range. Furthermore, in a subsequent paper, they elaborate on their plans for future research and development in this area.

The Synthetic Aperture Real-time Ultrasound System (SARUS) was developed and evaluated to facilitate synthetic aperture imaging, nonlinear imaging, and 3-D flow estimates [28]. The device had 1024 channels at a sampling rate of 70 MHz with a 12-bit resolution. The implementation of such a system entails significant expenses and involves complicated hardware and software design. Moreover, the considerable dimensions of this system impose limitations, while its lack of portability further hinders its practicality. One of the numerous advantages of ultrasound lies in its portability, particularly when in comparison with alternative procedures such as CT or MRI scanning. Ultrasound systems mostly consist of portable devices that may be conveniently transported to the patients' location within a medical setting, as well as to various test or inspection sites. Although this system serves as a research platform, its large size may hinder collaboration with other groups or departments due to limited mobility. The size of the system could be a result of the selection of the

transmitter circuit, for which there is little information available in references [29] and [30]. However, the use of an internally developed system has empowered the group to effectively pursue their specific objectives and modify the design to align with their preferences and budgets.

The Ultrasound Array Research Platform (UARP) [16] and its upgraded version, UARP 2.0 [31], were specifically developed to facilitate the investigation of various imaging methodologies, including harmonic imaging [32], and synthetic aperture imaging as well as non-destructive testing purposes (NDT) [33]. The system is based on 16-channel modules. Each module is equipped with a 1 GB DDR3 memory and a Stratix V FPGA. The excitation strategy described [34] is a highly effective design using metal-oxide-semiconductor field effect transistors (MOSFETs). The transmitter structure is based on 5-level switched mode excitation and works in the frequency range of 0.5 to 15 MHz; therefore, it does lack individual amplitude controllability and low lack in low-frequency usage (<0.5 MHz).

Additionally, to the previously mentioned technologies, there are other commercially available multi-channel systems [35], [36]. The Verasonics® engine has a high channel count, consisting of 256 elements for transmission and reception. It utilises tri-level pulsers, which operate with three distinct levels and offers the flexibility of programmable waveform parameters. Additional functionalities of the system encompass frame averaging and transmit apodization. The standard version of this device has a working frequency range of 0.5 to 20 MHz. A lower-frequency version is sold separately. Another example of a commercially available system is the LeCoeur developed by LeCoeur Electronique [37], which offers a maximum of 256 channels, adjustable sampling rates ranging from 10 to 80 MHz, and a high voltage analogue output of 120 Vpp. These systems, however, are designed primarily for imaging purposes and incorporate functionalities and hardware components that are unlikely to be used in therapeutic applications, hence substantially contributing to the overall cost.

To reduce focused beam distortion and skull absorption, it is necessary to use low frequencies, which provide enhanced penetration into the deeper parts of the brain [1], [38]. Several ultrasound-driving systems with therapeutic applications have been documented in the literature [39], [40]. However, publications lack comprehensive circuit diagrams that include specific component names and corresponding pricing for these systems. Hence, what

is currently available lacks accessible and affordable therapeutic circuits that can be used by therapeutic ultrasound arrays. This research gap highlights the need for developing specialized multi-channel driving systems tailored for therapeutic ultrasound applications that are cost-effective and capable of meeting the specific requirements of microbubble-based therapies.

3.2 Multi-element arrays for low-intensity ultrasound

Multi-element arrays are extensively used in focused ultrasound treatments. There exist various classifications of multi-element arrays, which can be broadly categorised into two distinct groups according to their respective construction techniques. The initial category involves the creation of arrays in which all elements are predetermined and cannot be changed or fixed. Certain arrays employ micromachining processes. One common practice in the fabrication of capacitive micromachined ultrasonic transducers (CMUT) involves the production of many units simultaneously [41]–[43]. After the planning of the size, form, and location of elements, the fabrication of all elements is carried out concurrently. The arrays often exhibit a planar configuration and possess compact dimensions. The investigation of designs for an array consisting of many flat arrays, each constituted of hundreds of elements, was conducted to enhance the practicality of CMUT arrays for drug delivery across the blood-brain barrier (BBB). However, no devices resulting from these designs have been reported so far [44]. These arrays are not readily available on the market and are not repairable in case of failure due to their built-in constraints. Nevertheless, the use of CMUT technology is limited to small-scale devices due to the challenges associated with acquiring a sufficiently large piezoelectric transducer (PZT) for our specific purpose. Moreover, it is possible that this approach could result in significant crosstalk between neighbouring parts or sections.

3.3 Aims and objectives

The main focus of this chapter was to explore whether the single-channel driver design developed in Chapter 2 could be used to operate a multi-element array and adapted into a larger multi-channel engine. Initially, an eight-channel driver was constructed, composed of eight individual single-channel drivers, and was assessed its performance. Eight single-channel drivers were produced using the same design methodology outlined in Chapter 2. A digital control unit was designed to control the amplitude, frequency, and delays of each channel. To verify the performance of all channels and anticipate their performance, we

evaluated the pressure and one-dimensional beam profiles generated by the piezoelectric transducer (PZT) of each transducer using a hydrophone. Next, the dome-shaped frame was fabricated using 3D printing. The PZT transducers were systematically arranged on this framework to construct the array. The array's acoustic performance was investigated, including waveform, focal pressure, beam profiles, and steering capabilities, in a free-field environment using a needle hydrophone. Subsequently, a single 16-channel PCB was designed for driving, along with separate 16-channel digital control unit PCB and 16-channel matching networks on separate PCB.

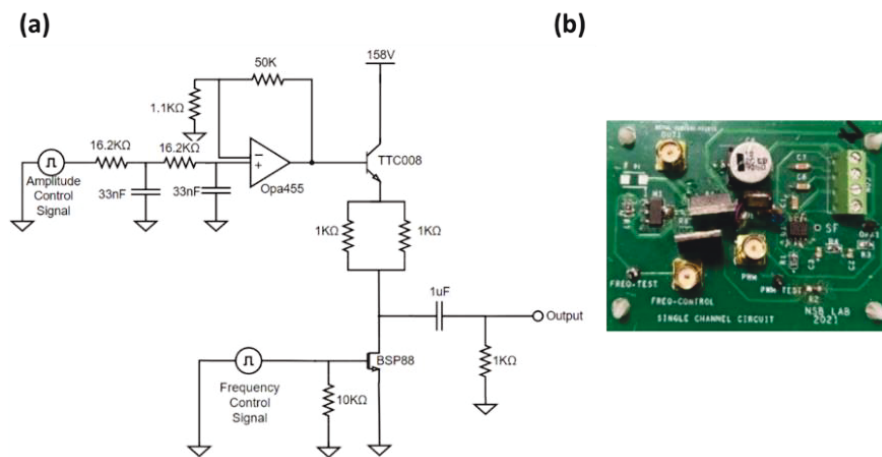


Figure 3.1. Single-channel high-voltage square wave pulse generator (HV Pulser). (a) A digital control unit (not shown here) dictates the amplitude via the amplitude control signal input (0-3.3 V) and the centre frequency, pulse length, and phase via the frequency control signal (0-3.3 V). (b) A populated printed-circuit board (PCB) of the design.

3.4 Materials and methods

3.4.1 8-Channel high-voltage driver system

The design of the individual channel driver was the same as the single-channel high-voltage driver presented in Chapter 2 (Figure. 3.1(a)). Eight transducers were assembled into a 3D-printed dome-shaped frame (Vero clear, Objet 30 Pro, Stratasys Ltd., Rehovot, Israel) to form an array (Figure. 3.2). A PZT/PVDF stacked transducers were used [4] due to their efficiency for our short-duration and therapeutic pulses in low-pressure. In brief, the transducer was made of a flat surface and consisted of many components, including a PZT disc operating at a frequency of 500 kHz (PZT-5/Navy type II/Pz27 from Meggitt A/S in Kvistgaard, Denmark), a PVDF receiver (with a thickness of 28 μm, sourced from Precision Acoustics (Dorchester,

U.K.) followed by two 3D printed matching layers and one 3D printed backing layer. Both the PZT disc and the PVDF layer had a diameter measuring 16 mm. This stacked structure allowed us to transmit and receive from the same location without compromising our broadband reception capabilities. The radius of curvature of the array was approximately 15 cm, equal to the natural focus of the transducers at 0.5 MHz. The elements were distributed approximately evenly on the array's curvature, into one concentric ring. The electric impedance of each PZT transducer in the array was measured by an impedance analyser (4395A Vector Analyzer, Agilent Technologies, Santa Clara, California, USA). Based on the measured impedances, a single inductor was used as a matching network despite the variations between elements. Eight of the single-channel drivers were connected to eight individual 120 μ H inductors as matching networks between the drivers and transducers to form an 8-channel driver [Figure. 3.3]. Individually controllable channels in terms of amplitude, frequency, delays, etc. (Table. 3.1.) were controlled via a digital control unit.

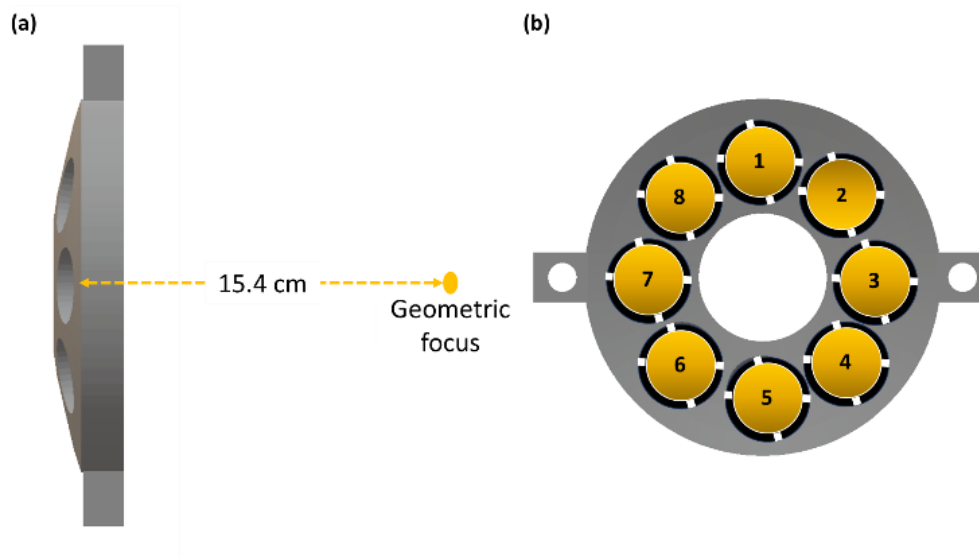


Figure 3.2. Structure of the eight-element array frame. (a) the lateral perspective of the dome-shaped array frame. (b) The frontal perspective of the array consists of 8 elements.

Table 3.1. Overall design specifications.

Frequency Range (MHz)	0.1-1
Output Voltage (V)	0-150
Voltage Adjustability (V)	7.5
Minimum Time Delay (ns)	15

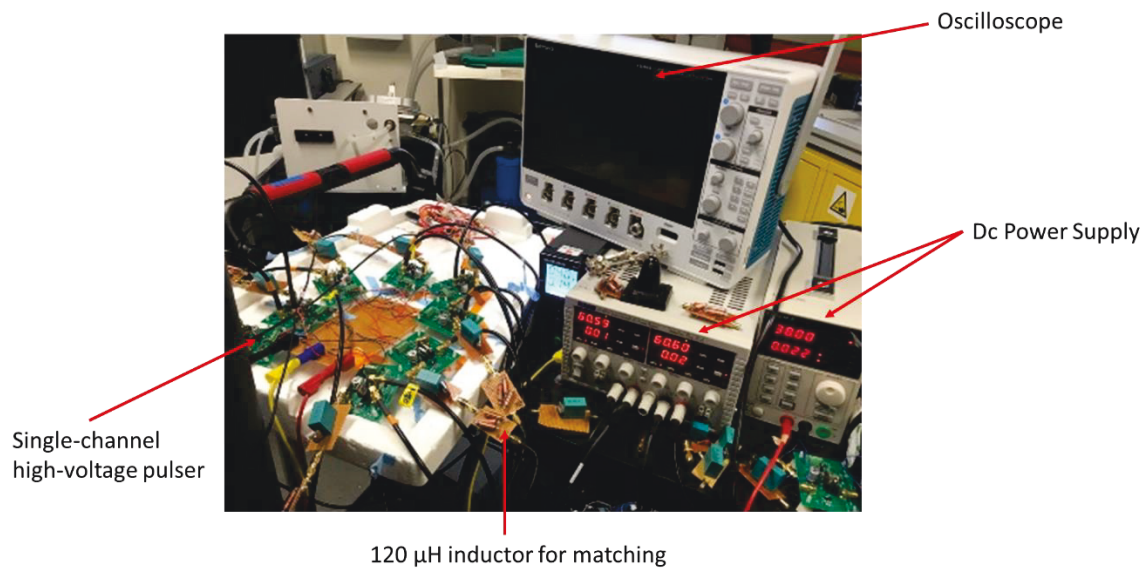


Figure 3.3. The 8-channel driver. Single-channel high-voltage pulsers were connected with a stripboard for DC supply distribution. Each channel was connected to a 120 μ H inductor for matching.

3.4.2 Digital control unit

The digital control unit determines the parameters of the square pulse generated by the high-voltage square wave pulse generator, including its amplitude, frequency, time delays, and pulse length. The controller board was created utilising Teensy 4.1 microcontrollers (PJRC, Sherwood, OR), ensuring programming simplicity, scalability, and cost. A master control board enabled communications between users and slave boards using i2c communication. The slave boards were responsible for controlling the high-voltage square wave pulse generator. In our design, each emitting channel was accompanied by a dedicated slave board responsible for regulating the emitting frequency, pulse length, and steering delay. Additionally, an extra slave board was incorporated to provide 10-kHz PWM amplitude-control signals for all eight channels. In this study, a total of one master board and nine slave boards were employed to facilitate an eight-channel excitation process, and for sixteen-channel excitation one master board and 17 slave boards were employed. So, a single PCB that contains 18 Teensy boards for 16-channel excitation (Figure. 3.4) was designed. The frequency and delay controlling slave boards were programmed with low-latency code, including non-operational loops and direct port manipulation techniques to ensure accurate timing. The experimental determination revealed that the precision of both the delay and frequency signal was within a margin of 15 nanoseconds. The operation of the drive system

was not affected by the timing of the amplitude control and master boards, and as a result, these aspects were not subject to monitoring.

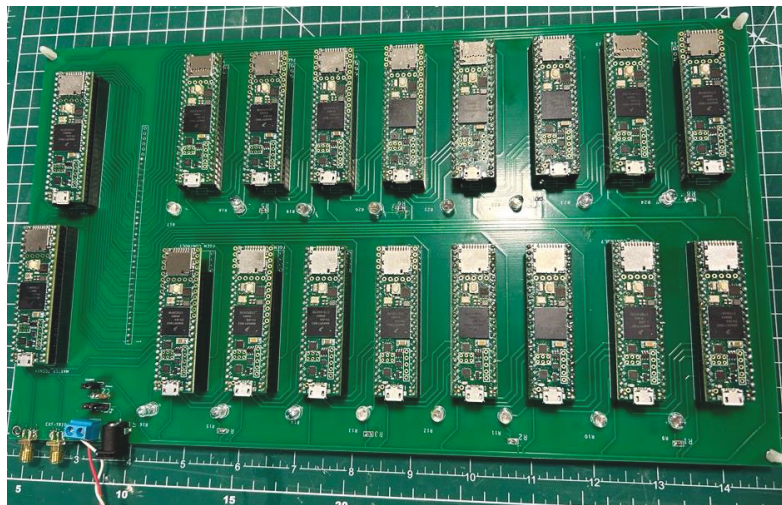


Figure 3.4. Digital control PCB for sixteen-channel excitation. One master board, one slave board for amplitude control, and 16 slave boards for frequency control were employed.

3.4.3 16- Channel high-voltage driver system

After building the 8-channel prototype using 8 separate single channels, a 16-channel driving system was built on a single board (Figure. 3.6). In the new PCB design for 16-channel driving, the modular structure similar to the single-channel PCB was kept. Sixteen transducers were assembled into a 3D-printed dome-shaped frame (Vero clear, Objet 30 Pro, Stratasys Ltd., Rehovot, Israel) to form an array (Figure. 3.5). The inner diameter of the array was 15.4 cm, equal to the natural focus of the transducers at 0.5 MHz. The active aperture size was also configured to be 15 cm. The elements were distributed approximately evenly on the array's curvature, into two concentric rings. This modular approach made it easy to construct and maintain the array. We could fabricate, test, and replace each component separately, ensuring that each component was working properly. Each transducer was connected to a driver channel in the 16-channel PCB. A single PCB was designed for a 16-channel array driver and a separate PCB was designed for 16 matching networks (120 μ Hz) despite some impedance variation between elements (impedance variation between elements was measured as 382 Ω -403 Ω). The PCB for the matching networks had 4 high-voltage protection T/R switches (MD0101, Microchip, Arizona, USA) that allowed simultaneous reception between emissions (Figure. 3.7). When the voltage across Terminals TX and RX exceeds 2V,

the switch transitions into Transmit mode, which blocks the transmission of the high-voltage pulses to the receiving end.

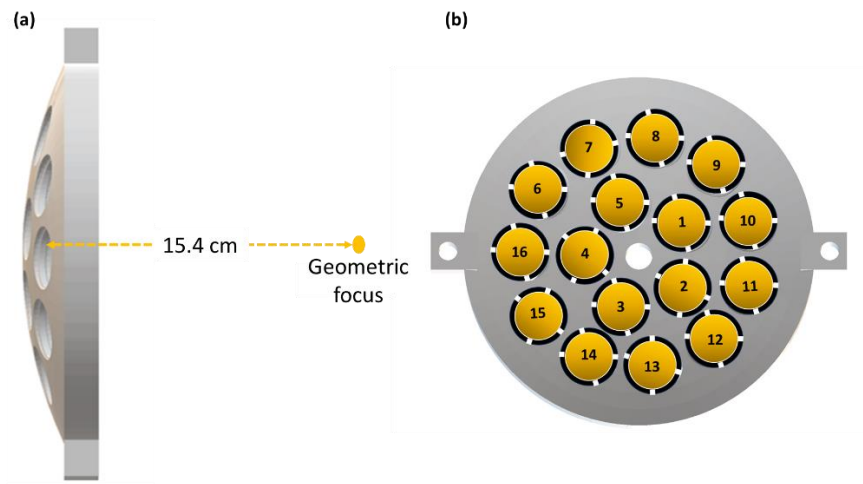


Figure 3.5. Structure of the sixteen-element array frame. (a) the lateral perspective of the dome-shaped array frame. (b) The frontal perspective of the array consists of 16 elements.

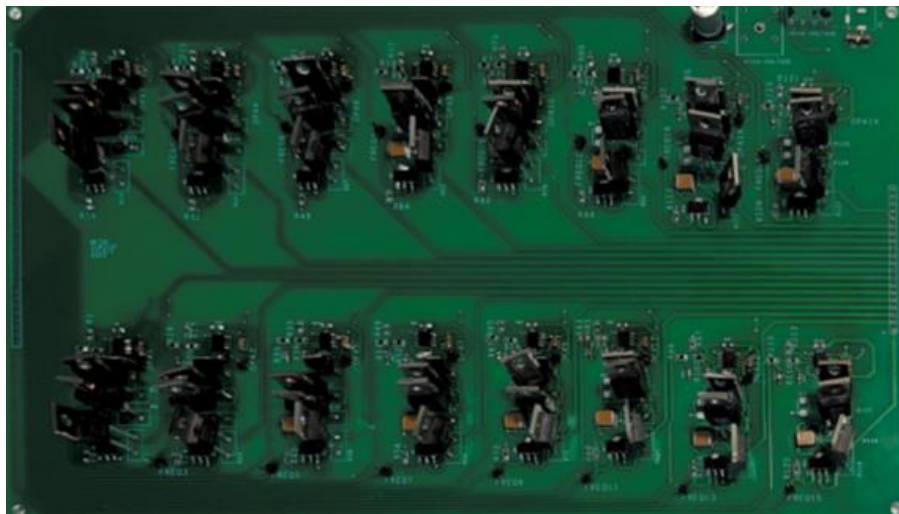


Figure 3.6. Sixteen-channel high-voltage square wave pulse generator (HV Pulser) populated on a printed circuit board (PCB).

The 16-channel driver was supplied by two DC supplies (Aim-TTi CPX400D 420W, Cambridgeshire, United Kingdom, and TENMA T2-2935) at 150V. Every channel was given the same amplitude control signal at 50% duty cycle (nominally 75V to the transducer) during beam focusing and steering experiments. The excitation frequency was 0.5 MHz, and the pulse length was 5 cycles. Because the array was assembled by hand, the positions of the transducers may not be arranged on a perfect curve, i.e., there may be small variations of

the distances between different transducer surfaces and the geometrical centre of the array. These uncertainties were compensated by applying an appropriate time delay determined by testing with a hydrophone between each transducer.

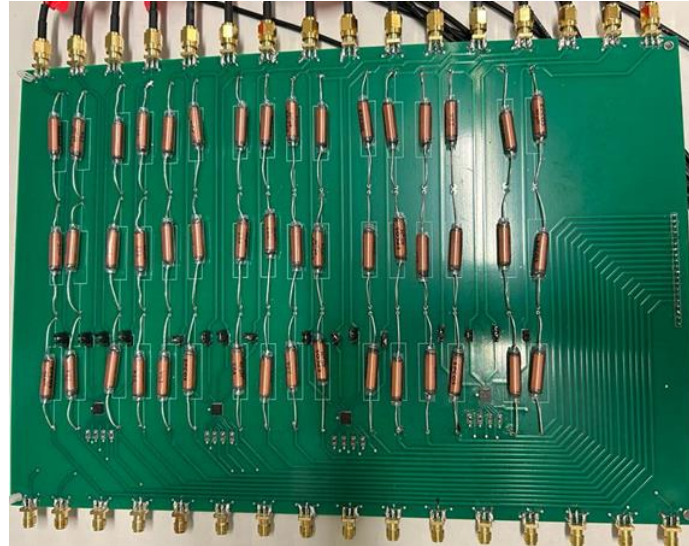


Figure 3.7. Sixteen-channel matching network with T/R switch populated on a printed circuit board (PCB).

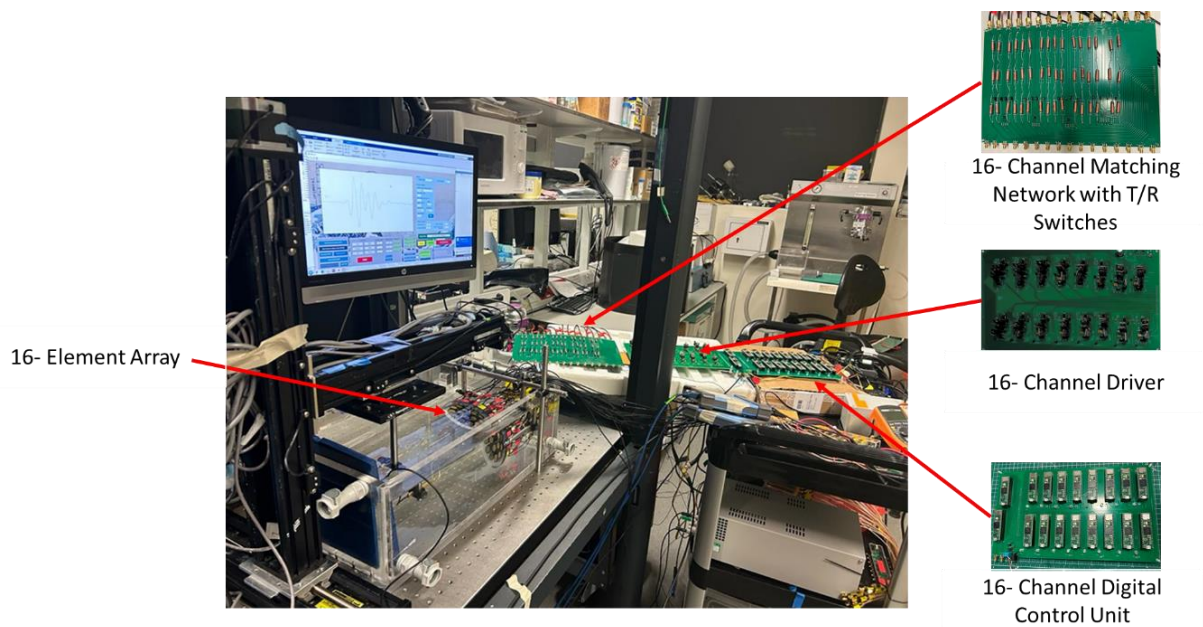


Figure 3.8. The complete 16-channel driver system with 16-element array. The 16-channel driver generated excitation that went through the 16-channel matching network before reaching the PZTs to generate ultrasound. The parameters for the excitation signal were sent through MATLAB via the digital control unit.

3.4.4 Electrical characterization

The electrical responses of the individual drivers were tested without connecting the transducer as a load to understand the behaviour of the driver (e.g., loading effect) and measure the linearity of the controllable amplitude control output between channels. Two function generators (Keysight; 33500B) were used to generate the digital input signals. Different amplitude control signals (duty cycle: 5% to 99%, frequency: 10 kHz) and frequency control signals (20 cycles, 0.1-1 MHz) were generated and fed to the high-voltage driver circuit. The output of the circuit was recorded using an oscilloscope (Tektronix MDO3000 Mixed Domain Oscilloscope, Tektronix Inc.) with a high-impedance probe.

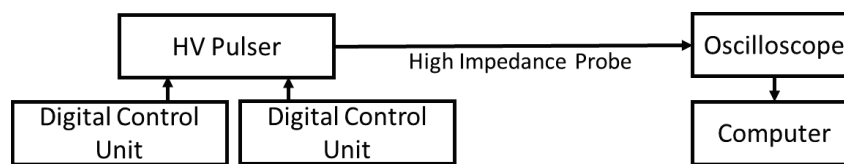


Figure 3.9. Experimental setup for electrical characterization. Each channel was tested in the 8-channel high-voltage driver system and 16-channel high-voltage driver system without a transducer connected as a load. Two function generators were used to control the amplitude and the frequency/delays/number of cycles of the signal. The generated square waves in different settings were observed by using a high-impedance probe, and data was collected by an oscilloscope. The duty cycle of the amplitude control signal was varied from 5% to 99% for four different frequencies namely 0.1 MHz, 0.3 MHz, 0.5 MHz, and 1 MHz. All of the channels were tested individually in the same way.

The performance of the digital control unit was tested in terms of different delay, frequency and number of cycles using an oscilloscope (Tektronix MDO3000 Mixed Domain Oscilloscope, Tektronix Inc.).

3.4.5 Acoustic characterization: individual-channel characterization

The performance of the circuit in conjunction with a transducer (loaded condition) was tested in a tank filled with deionized and degassed water (Figure. 3.10). A custom-made 0.5MHz PZT transducer was used for emission. The PZT was excited with 5-cycle pulses at 0.5MHz by our high-voltage drivers one by one with and without a matching network connected. The amplitude of the signal was varied using a duty cycle between 5% and 99% to evaluate the pressure variation between channels. The transmitted ultrasound pulses

travelled 15 cm away from the transducer and were captured by a commercial 1-mm-in-diameter needle hydrophone (Precision Acoustics, Dorchester, U.K.) placed on a 3D-positioning system. The measurement was conducted at a distance of 15 cm from the surface of the PZT transducer in order to replicate the natural focal distance of both 8-element and 16-element systems. Before performing the test, the hydrophone was initially displaced along both lateral axes in order to identify the precise position at which the highest pressure could be detected. The received signal was then digitized by the oscilloscope mentioned previously, before being stored on a computer. All channels were tested individually.

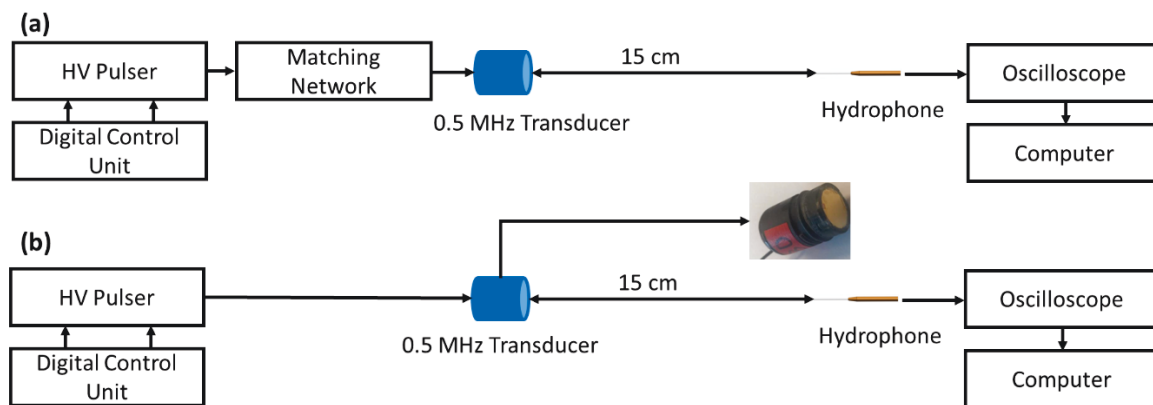


Figure 3.10. Experimental setup for evaluating the performance of each channel driving a single transducer (a) with a matching network connected and (b) without a matching network connected. The 1-mm hydrophone was placed 15 cm away from the transducer. The PZT transducer was excited by our high-voltage drivers from 8-channel and 16-channel drivers controlled with a digital control unit. The generated ultrasound field was measured by a needle hydrophone. The received signals were digitized before being stored on a computer. The performance of all 16 channels was tested on the same setup.

3.4.6 Acoustic characterization: electronic beam focussing and steering

The acoustic performance of the 8-channel driver and 16-channel driver with the relevant arrays were assessed using a 1-mm needle hydrophone, which involved analysing various aspects such as pressure, waveform, beam focussing, and beam steering. The tests were conducted inside a water tank that was filled with degassed and deionized water. First the 8-channel driver which consists of eight single-channel drivers to excite the 8-element array (Figure. 3.11 (a)) were used. A needle hydrophone with an active diameter of 1 mm, manufactured by Precision Acoustics in Dorchester, U.K., was fixed to a 3D-positioning

system. This setup allowed for the scanning and measurement of the ultrasonic field produced. The signal received by the hydrophone was converted into digital form and subsequently stored using the previously mentioned oscilloscope with a sampling rate of 100 MHz. Then the same setup and tests were repeated with the 16-channel driver and 16-element array (Figure. 3.11 (b)).

Initially, the hydrophone was positioned at the geometric centre of the array, corresponding with its natural focal point. Subsequently, each of the elements from the 8-element array was individually excited with our 8-channel driver at 0.5 MHz and 5-cycle 50 % duty cycle amplitude. The hydrophone detected the 8 signals that were individually generated. The time delay of each channel was determined using a MATLAB-based script that calculated the time-of-arrival of the 8 signals. The implementation of a time delay can effectively synchronise an ultrasound emitted by the 8-channel driver, ensuring that they converge at the focal point simultaneously and in phase. Trigger delays equal to the difference in the time of flights were then applied to the respective channels. The identical procedure was executed consistently whenever there was a need to adjust the focus, such as steering. We also followed the same methods for the experiments with the 16-channel driver and 16-element array.

After applying the appropriate time delay, the pulse waveform generated by the array was acquired at the array's geometric centre. The duty cycle of the amplitude control signals was increased with 10 % increments from 10 % to 90 % duty cycle to find out the upper limit of the focal pressure. The hydrophone was employed to conduct a comprehensive raster scan throughout a substantial region in order to acquire the beam profiles of the 8-element and 16-element arrays while specifically focusing on the geometric centre. For the 8-element array, a raster scan was made in the axial plane of the array (15-by-15 mm, 0.5 mm pitch). The scan was done using the same needle hydrophone previously described, which was connected to a 3D positioning system. The raster scan was repeated when the needle beam moved 5 mm in the lateral direction to demonstrate the driving system's performance on beam steering. For the 16-element array, both axial and lateral scans for the different locations of the beam were performed.

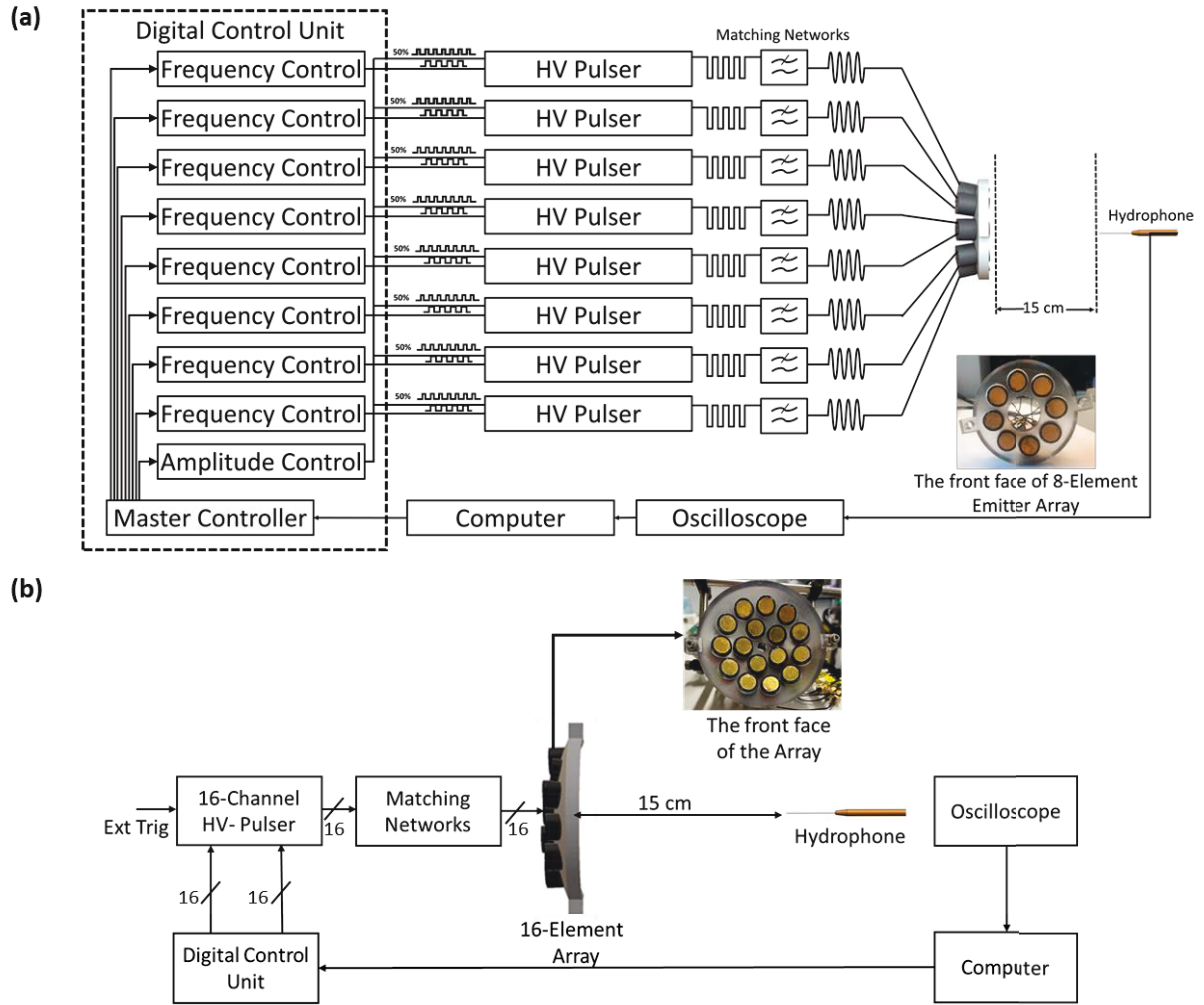


Figure 3.11. Experimental setup for characterising electronic beam focussing and steering with an (a) 8-element and (b) 16-element system. (a) An 8-channel driver made of eight single-channel drivers was used to drive an in-house-built 8-element array. (b) A 16-channel driver was used to drive an in-house-built 16-element array. Ultrasound pulses were captured with a 1-mm-in-diameter needle hydrophone fixed on a 3D-positioning system located 15 cm away from the array.(Array and array elements designed by a former PhD student, Zheng Jiang).

3.5 Results

3.5.1 Electrical characterization: individual-channel characterization

The performance of each driving channel after varying the output frequency, amplitude, and number of cycles was evaluated. First, the 8-channel driver which was made of single-channel drivers connected was tested. Our 8-channel driver without matching networks connected, had linear amplitude responses between 0.1 and 1 MHz (Figure. 3.12 (a)). The

PWM-controllable amplitude output produced low variations between channels. The highest variations were observed at 1 MHz, which was the highest frequency evaluated. 8-channel drivers were tested without the consideration of the settling time of the low-pass filters and that caused the amplitude variations between channels in high frequency for higher duty cycles.

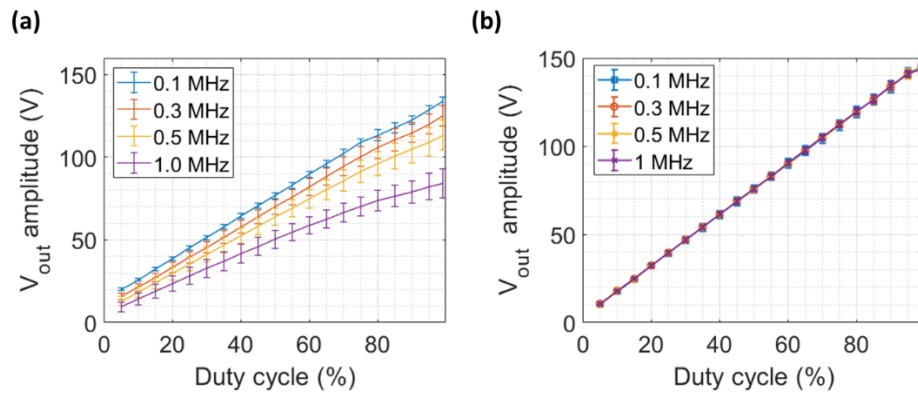


Figure 3.12. Electrical testing revealed the output voltage vs duty cycle relationship for individual drivers of (a) an 8-channel system and (b) a 16-channel system. The duty cycle was varied from 5 to 99% and frequency was varied from 0.1 to 1 MHz without a matching network connected. Each duty cycle was sonicated 3 times.

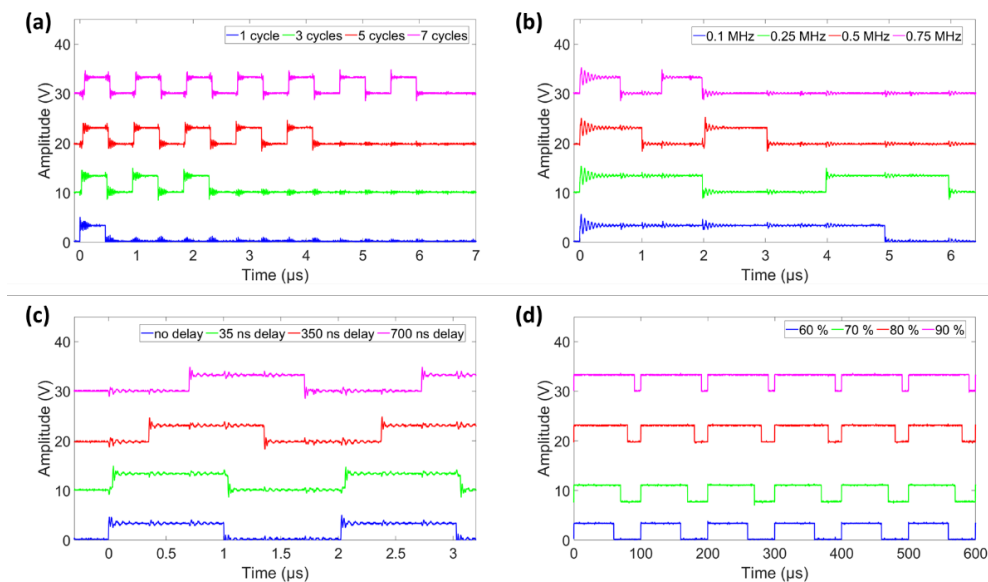


Figure 3.13. The performance of the digital control unit. The output of the digital control unit was captured with an oscilloscope for different (a) numbers of cycles (b) frequencies (c) delays and (d) duty cycles.

Then, the 16-channel driver's performance was tested when there was no transducer connected. the duty cycle from 5 % to 99 % was varied for frequencies from 0.1 MHz to 1 MHz. In this experiment, 2 seconds were waited for each amplitude change and measured the output. Very low variations between channels were observed, and the response was linear. To calibrate the output of the digital control unit, multiple experiments were run. Each parameter was tested in more than 10 trials. No noticeable timing change was observed during 10+ trials. The control unit was able to generate a precise 15ns delay. The small differences in the signal amplitude between consecutive pulses, particularly in the dynamic component, are likely due to a combination of noise, signal generation and measurement inaccuracies, and environmental factors.

3.5.2 Acoustic characterization: individual-channel characterization

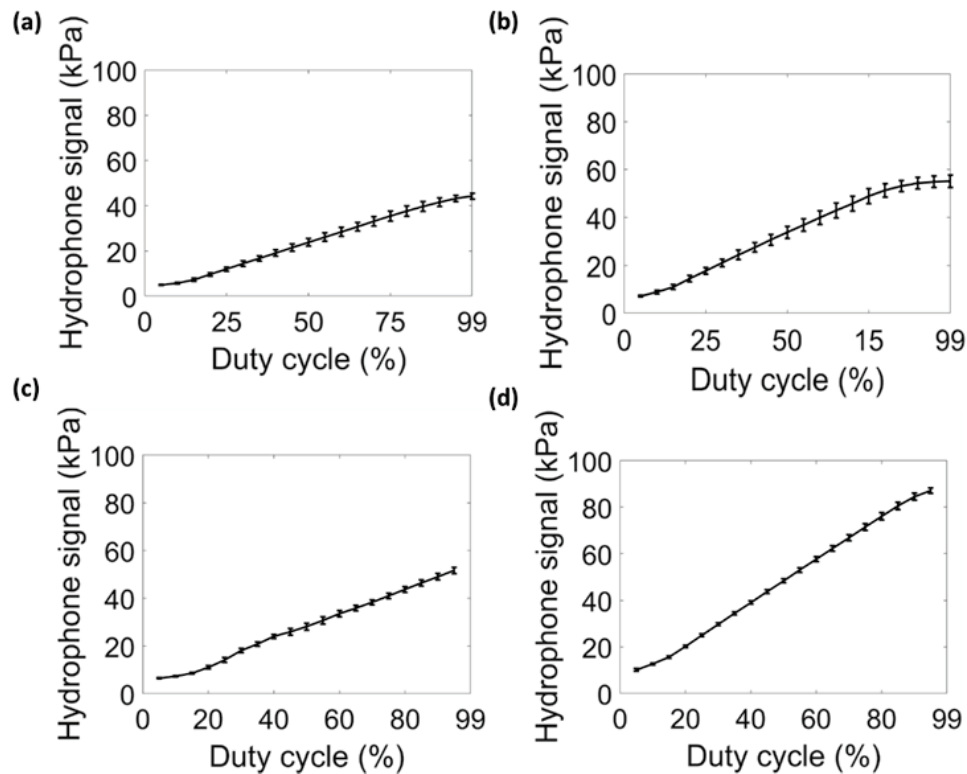


Figure 3.14. Acoustic testing demonstrated the output pressure vs duty cycle relationship for each of the (a, b) 8 single-channel drivers and (c, d) 16-channel drivers. A PZT transducer was excited in a water tank by each channel applying a 0.5 MHz and 5-cycle pulse both (a, c) without and (b, d) with a matching network connected. Ultrasound pulses were captured with a 1-mm-in-diameter needle hydrophone fixed on a 3D-positioning system located 15 cm away from the transducer's surface. All 8 channels and 16 channels were excited three times and the PNPs were averaged for each duty cycle individually using the same transducer.

All channels were tested separately in the same experimental setup (Figure. 3.11). Since a narrow-band PZT transducer was used for this experiment, only a single centre frequency of 0.5 MHz was evaluated. Thus, the amplitude control was evaluated by varying the duty cycle of the digital amplitude control signal. For each channel in the 8-channel driver and 16-channel driver, the 0.5MHz PZT transducer was excited with 5 cycles with and without the matching network connected. The acoustic pulses were captured by a 1 mm needle hydrophone (Precision Acoustics, Dorchester, U.K.). The acoustic pressure amplitude of the captured signals in both cases (with and without a matching network connected) increased linearly for the duty cycle above 5%. At duty cycles below 5%, the amplitude remained constant. For all channels, the pressure increased when the matching network was connected. At duty cycles between 0% and 5%, the captured signals did not increase linearly with the duty cycle in both cases. This was most likely because the MOSFET switch did not remain in the saturation mode of operation due to having so small voltage at its drain terminal. Therefore, we can only expect the duty cycle range from 5% to 99 % to have a linear response.

We also observed that the channels in the 16-channel driver had increased output pressure compared with the 8-channel driver. The 8-channel driver was made of single-channel drivers connected with some cables. We expected this reduction in pressure due to the cable loss in the 8-channel driver. In both drivers, matching networks increased the pressure output. But in the 16-channel driver, the matching network increased the output by %60 compared to without the matching network.

3.5.3 Acoustic characterization: overall waveform, electronic beam focussing and steering

When we excited the 16-element array with the 16-channel driver at the geometry centre, we varied the duty cycle from 10 % to 90 %. We obtained around 0.6 MPa pressure which is sufficient enough to induce bubble cavitation at the 90 % duty cycle (Figure. 3.14).

First, the performance of the system for focusing ultrasound at the geometrical centre of the curved 8-channel array was tested. The array was able to generate a tight focus at its geometry centre in the free field (Figure. 3.16 (a)). The full width at the half-maximum (FWHM) of the focus was approximately 5.1 mm in diameter. Some grating lobes were seen around the main beam. The maximum of approximately 320kPa pressure was obtained by using our 8-channel driving circuit by using the 8-element array in the free field.

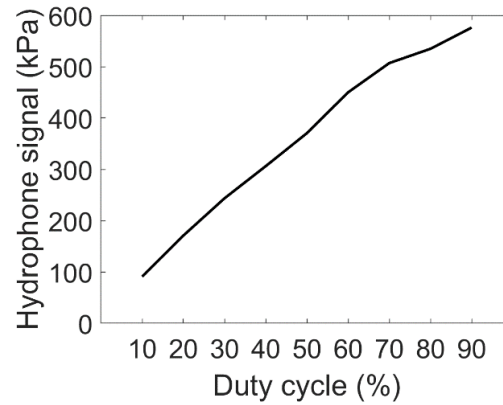


Figure 3.15. The relationship between the PNP and the duty cycle of the 16-element array driven by the 16-channel driver. A needle hydrophone was placed at the geometric centre of the 16-element array. The duty cycle used to control the 16 drivers was adjusted between 10% and 90%, which increased the PNP at the focus. Each duty cycle was sonicated 3 times.

When the focus was steered by 5 mm in the x-direction, the FWHM of the main beam stayed approximately constant. The grating lobes around the main focus had a similar amplitude as those without steering. More grating lobes were observed in the direction opposing the direction of the steering (Figure. 3.16 (b)). We only steered the beam on the x-axis and performed an axial beam scan.

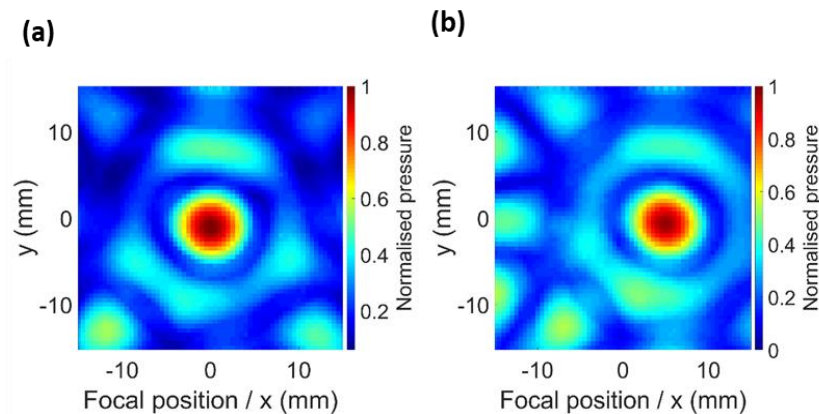


Figure 3.16. Beam profile for the 8-channel driving circuit with an 8-element array. Using the 8-channel driver to drive an 8-element ultrasound array, a focal beam could be formed (a) at the geometric focus and (b) at 5-mm away from the geometric focus along the x-axis. Beam steering was performed by applying time delays using the 8-channel driving circuit. Beam profile measurements were performed using a 1-mm-in-diameter needle hydrophone with a raster scan.

Then we tested the performance of the 16-channel driver with a 16-element array to focus the ultrasound beam at the geometrical centre. The array was able to generate a tight focus at its geometry centre in the free field (Figure. 3.17 (c)). The full-width at the half-maximum (FWHM) of the focus was approximately 4.9 mm in diameter. Some grating lobes were seen around the main beam. The maximum of approximately 600kPa pressure was obtained by using our 16-channel driver using the 16-element array in the free field. Increasing the number of channels reduced the beam size, which will allow more precise targeting.

With a 16-channel driver, the focus was steered by 5 mm (Figure. 3.17 (b)) and 10 mm (Figure. 3.7 (a)) In the x-direction, the FWHM of the main beam stayed approximately constant. The grating lobes around the main focus had a similar amplitude as those without steering. More grating lobes were observed in the direction opposing the direction of the steering (Figure. 3.17 (a)).

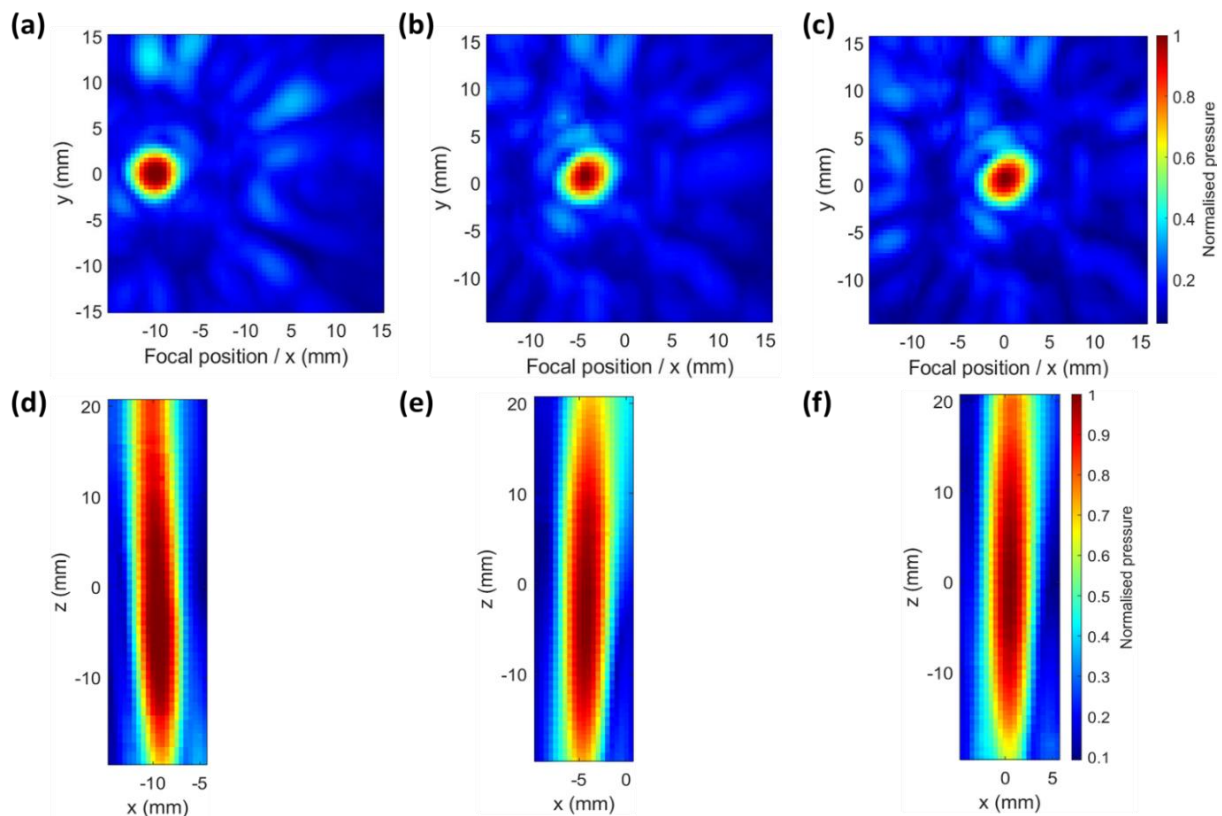


Figure 3.17. Beam profiles of 16-element array when focusing and steering on the x-axis.

Beam profiles at the (c), (f) geometry focus and when the focus was steered along on the x-axis by (b), (e) 5 mm and (a), (d) 10 mm.

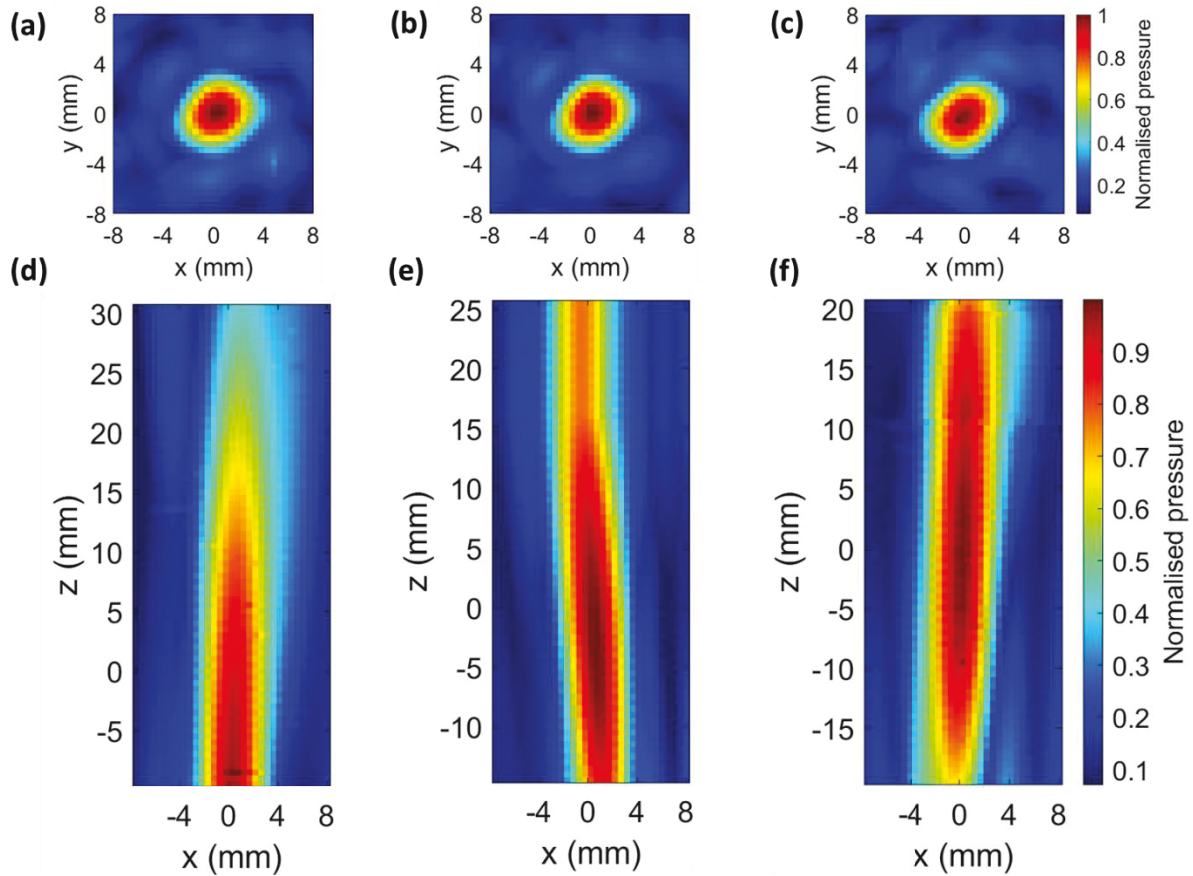


Figure 3.18. Beam profiles 16-element array steering the focus on the z-axis. Beam profiles when the focus was at (c), (f) geometric centre and when the beam was steered by (b), (e) 5 mm away from the transducer and (a), (d) 10 mm away from the transducer.

3.6 Discussion

3.6.1 Electrical characterization

A low-cost multi-channel ultrasound driver system for therapeutic array applications were demonstrated. Both 8-channel and 16-channel driving systems were capable of focusing and steering an ultrasound beam at a therapeutically relevant frequency. Individual channels were separately controlled by a digital control unit in terms of amplitude, frequency, number of cycles, and delays. The driver was characterized by performing electrical and acoustic tests.

The production of unipolar pulses was chosen over bipolar or multi-level pulses out of simplicity and to reduce the cost of the system by using fewer components. By using a high driving voltage (150V), the driver was able to produce sufficiently high pressures comparable to those produced by bipolar pulses for microbubble-based therapies. The individual channel

amplitude controllability feature was retained, enabling the production of arbitrary waveforms from a multi-element array.

When testing channels individually, we observed that the output voltage decreased with increasing frequency in the 8-channel driver. This decrease was likely due to connection losses, as the 8-channel driver was made of eight single-channel drivers connected with wires. This effect was not observed in the 16-channel PCB. Our driver's working frequency was limited to 1 MHz due to a high overshoot when the frequency was increased beyond this point. This limitation is attributed to the chosen MOSFET switch's fast rise and fall times and the BJT's high switching time (storage time). To improve the working frequency range, a faster BJT could be used, and gate drivers could be implemented for the MOSFET to enhance switching frequency, all while considering cost constraints.

We only tested one type of matching network for the array due to simplicity and affordability, but optimizing the design of the matching networks could increase the pressure amplitude while still removing unwanted harmonics. To further reduce costs and allow more precise controllability, the digital control unit could be upgraded to a combination of microcontrollers with FPGAs, although this would increase programming complexity. The interchangeability of components in our design and their overall low cost enables significant scope for experimentation and fine-tuning of the system for desired applications.

The driving system was designed with affordability as a key requirement. The 16-channel prototype cost on average \$32 per channel (including operational amplifier, BJT, MOSFET: \$10; matching network: \$2; microcontroller: \$20). For higher element counts, the microcontroller boards could be replaced with an FPGA or other digital control units to reduce overall costs. We estimated that scaling our driver to 128 channels would cost approximately \$1600, excluding the cost of the power supply and controllers. Thus, the design presented here is affordable and has good scalability.

When comparing our system to other custom-built or commercial systems, our design stands out for its cost-effectiveness and modularity. Commercial systems often provide a higher frequency range and more advanced control features, but at a significantly higher cost, often exceeding \$100,000 for a comparable number of channels. Custom-built systems in research settings may achieve higher pressures and frequencies but frequently lack the scalability and

ease of component interchangeability that our design offers. The ability to produce therapeutically relevant pressures and the flexibility of our system make it a valuable tool for various ultrasound-mediated therapies.

3.6.2 Acoustic characterization

Results of our beam focusing and beam steering experiments show that therapeutically relevant acoustic pressures can be produced with our multi-channel driving system, especially with an increased number of channels. For example, delivering drugs across the blood-brain barrier typically requires an acoustic peak-rarefactional pressure of 0.4 MPa and a pulse length of 5 cycles. Increasing the number of channels in our system could produce such pressure across the human skull.

Our single-channel driver can produce pulses with a maximum amplitude of approximately 150 V. Each PZT transducer, with a low-pass filter and without a matching network, can produce an average pressure of 85 kPa at maximum excitation amplitude. At 0.5 MHz, only 20% to 30% of the pressure can pass through the human skull to reach the sonication region within the brain parenchyma [45]–[47]. Assuming a linear increase in output pressure with an increasing number of channels, a minimum of 25 channels are needed to produce 400 kPa to deliver drugs to the brain. Improving the matching networks for the array and increasing the number of channels could make our ultrasound driving system efficient enough to steer an ultrasound beam to different regions of the brain. Considering its low cost and modular approach, such scalability is highly feasible.

The device had a good focusing ability, with the flexibility to electronically steer to a target position with a broad focus offset, providing promising scalability and efficiency in localizing exposure of the brain to ultrasonic energy. Even when considering the natural focal point (geometric centre of the array), we needed to implement time delays between channels. This observation can be attributed to the flaws present in both our transducer and array design. If the precise distances between each element and the geometric centre of the array shape were known, there would be no requirement for any time delay when focusing on the geometric centre. However, in our experiments, we needed to apply relevant time delays for focusing at the geometric centre.

The steering range defined in this study represents the maximum distance to which the focus can be directed without the occurrence of additional peaks in pressure exceeding 50% of the primary focus. [2], [48]–[50]. When we steered the beam by 10 mm, the secondary maximum was smaller than 50% of the primary focus, and we did not observe any focal volume change. We did not perform the full steering range test for the array, as it is more related to the design of the array than the driver design. The array can produce a tight focus with a full width at half maximum (FWHM) dimension of $4.9 \times 4.9 \times 40$ mm in free-field. This focus was observed in free-field, and we expect the FWHM size to increase in actual therapy with a patient due to the presence of the skull [50].

3.7 Conclusion

We designed and constructed a 16-channel low-intensity driver and evaluated its acoustic performance with a stacked PZT-PVDF array. The 16-channel drivers' performance was tested with a single transducer individually to observe the variation between channels. The use of a modular assembly architecture facilitated easy repair and replacement of individual components, enhancing the cost-effectiveness of array and driver maintenance. A randomization technique was implemented on element arrangement in the array to improve its performance.

Systems for ultrasound-mediated therapies must meet specific design specifications to improve treatment efficacy and safety. These include a large number of channels, sub-megahertz frequency output, and potentially short ultrasound pulses. Existing multi-channel driver systems either cannot satisfy all these requirements or are too expensive due to features designed for imaging applications. Our low-cost, highly scalable, multi-channel driver system addresses these gaps by producing sub-megahertz pulses of arbitrary lengths.

The prototype's performance was investigated experimentally in single-channel mode and an array of 8/16 PZT/PVDF stacked transducers. Control over frequency, amplitude, and beam focusing/steering was demonstrated. This simple design can be scaled to a very large number of channels at a relatively low cost, facilitating more cost-effective research. We estimate that the overall cost of a 128-channel driver circuit, excluding the power supply and control unit, would be less than \$1600. When combined with rapid 3D-prototyping methods

for making ultrasound transducers, our low-cost circuit could make therapeutic ultrasound array technologies more widely accessible and ubiquitous.

Our system's key contributions to novelty include the affordability of the driver circuit, its modular and scalable architecture, and the flexibility in control and customization for various therapeutic applications. This innovation significantly lowers the barrier to entry for researchers and clinicians looking to utilize advanced ultrasound techniques in therapeutic settings.

3.8 References

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4 The design and optimization of a programmable/dynamic network

4.1 Introduction

Piezoelectric devices are used for emission and reception purposes in a diverse array of applications. Specific applications such as high-intensity focused ultrasound therapy, imaging, and blood-brain barrier disruptions require careful design of sensor/actuators and driving electronics due to the critical nature of the tasks these devices perform. Some of these applications perform detection of damage/defects, delivering drugs into precise locations of the body or removing cancerous tissue. Therefore, the efficacy of the emission and reception system is very important.

A high electrical impedance of the transducer leads to a significant impedance mismatch between the transducer and connected devices, such as drivers or data acquisition systems resulting in a significant amount of energy reflection, which can result in excessive energy consumption and consequent harm to the electronic equipment connected. This includes significant heating of the driver, which can lead to permanent damage to its components. It also results in a decrease in the amplitude and waveform of the signal, leading to a reduction in the signal-to-noise ratio (SNR) and the presence of damage features based on the waveform. This issue can be mitigated through the implementation of an Electrical Impedance Matching Network (EIMN) [1]–[3]. In the context of impedance matching, it is common to address both acoustic and electrical aspects [4]. The implementation of acoustic impedance matching (AIM) enhances the performance in narrowband applications, however resulting in an increased level of the electrical impedance.

The design approaches used by the matching networks for piezoelectric transducers mostly consist of analytical methods [5], [6] and CAD methods [7]–[9]. The complexity of the analytical approach requires the use of the analytical form of the transducer, hence imposing limitations on its application within the field of engineering. CAD approaches have the potential to address the constraints of analytical methods. However, determining the appropriate topology for optimization creates challenges in a variety of complex problems [6], [10]. The availability of a singular, specialized tool for designing EIMN is limited due to the variability of the design process, which is dependent on the specific application and

power needs. A lot of applications require broadband or multi-frequency working range, and this is only achievable using various or variable components in the EIMN.

Broadband EIMNs can be effectively developed with the Smith chart through the careful selection of an appropriate quality factor (Q) constraint. However, it is necessary to experiment with a range of different topologies and subsequently ascertain the optimal one. Furthermore, it should be noted that the assumption of a negative correlation between the Q factor and bandwidth becomes invalid in cases when the transducer's impedance exhibits several peaks and undergoes significant variations. Based on the above discourse, it can be inferred that additional study is required to determine the optimal methods for designing EIMNs with both effectiveness and efficiency. Furthermore, there is a limited number of studies that address the issue of matching issues between transducers and active loads, such as power amplifiers (PA). Current research on the design of EIMN mostly focuses on obtaining impedance matching between sensors/actuators and interface devices, such as signal generators and receivers. These interface devices typically possess a fixed impedance of 50Ω [1], [11]–[13]. The impedance matching between the transducer and PA exhibits notable distinctions, primarily stemming from the nonlinearity and dynamic nature of the PA's output impedance.

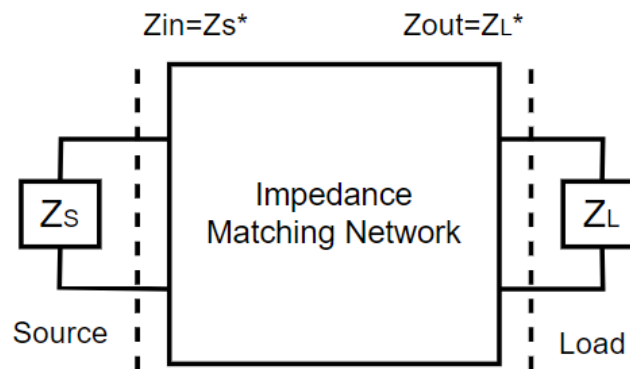


Figure 4.1. Conjugate matching of input and output impedance via a two-port Electrical Impedance Matching Network.

Impedance matching could be divided into two fundamental components, namely resonance/conjugate and resistance matching/reflectionless matching. Based on the maximum power transfer theory, the delivery of maximum power from a source to a load occurs when the transducer's impedance is a complex conjugate of the amplifier's

impedance in a two-port system (Figure 4.1). The resonance matching could be achieved by using a simple LC network, also known as a shunt inductor/capacitor configuration to perform oscillations with the transducer's parallel capacitor [11], [14]. In order to reduce the possibility of reflections, it is necessary to maintain equal impedances between the input and output ports. This is called reflectionless matching. The real impedance of the transducer can be matched to the source via a transformer [15], [16].

Therapeutic ultrasound where the transmission efficiency is important as well as the minimized reflection, there is almost always a matching network used between the ultrasound probe/transducer and the excitation circuits. The majority of conventional piezoelectric transducers exhibit narrowband characteristics, limiting their ability to generate significant vibrations to a narrow range near their resonant frequency. An increasing number of applications require the use of transducers that operate within a broad spectrum of ranges. Several recent studies have concentrated on the design methodologies of broadband piezoelectric transducers [17], [18] or dual frequency transducers [19]–[21]. Regarding broadband piezoelectric transducers, it is worth noting that the techniques employed for developing broadband electrical impedance-matching networks tend to be complex and hard to fully understand. While various approaches for constructing EIMNs have been established [1], [9], it remains vital to identify a strategy that is both feasible to implement and exhibits desirable performance. Due to the requirement of transmission efficacy and minimized reflections, commercially available transducers used in therapeutic ultrasound came with an expensive matching network for each excitation frequency. (£1000). Therefore, it is not cost-effective in the long term. There is a need for a cost-effective alternative for a matching network that can be used with multiple transducers for a broader range of frequencies.

4.1.1 Determining the equivalent circuit models for transducers and simulation tools

The piezoelectric ultrasound transducer is often analysed using different equivalent circuit models, including the KLM [22], [23], Mason [24], Redwood network [25], and Butterworth-Van Dyke (BVD) [26] models. The selection of a model is based on the particular application and the type of system being considered. The KLM model requires a combination of physical factors such as dimensions, thickness, and coupling material, which are used to derive equations for quantifying insertion loss and pulse-echo. The use of this technique proves to

be particularly advantageous in enhancing the efficiency of transducers, and its application can be observed in software platforms such as PiezoCAD [27]. In contrast, BVD models simply require the use of impedance and admittance, allowing their implementation with lumped components rather uncomplicated. The integration of EIMNs with similar circuit models enables the simulation of a matching ultrasonic transducer.

OrCAD PSpice A/D [28] is often used in the evaluation of the matched transducer's performance through the application of AC simulation capabilities. Studies carried out with high-frequency and broadband ultrasonic transducers frequently use PSpice [1], [29], a software tool, to analyse and evaluate the gain and bandwidth of the matching network. This is achieved by comparing the responses of transducers that are matched and unmatched. The investigation can also encompass variations in the component values of the EIMN, as well as the impedance of both the load and the source.

The Butterworth-Van Dyke (BVD) model is a common technique for modelling piezoelectric transducers [29]. This model is often derived from evaluating the impedance or admittance measurements of the transducer. The BVD model contains the mechanical components (R_s , L_s , C_s) and the electrical component (C_0) of the transducer. C_0 denotes the equivalent capacitance, R_s represents the combined losses due to radiation and mechanical factors, and L_s and C_s are used to represent the resonant behaviour of the transducer (Figure 4.2).

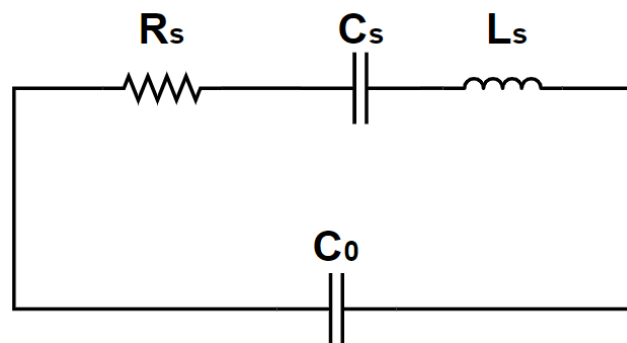


Figure 4.2. Single-frequency Butterworth-Van Dyke (BVD) model for piezoelectric transducer.

The admittance exhibits its maximum value at its series resonance, whereas it demonstrates its minimum value at the point of parallel resonance.

Series resonance radial frequency,

$$\omega_s = \frac{1}{\sqrt{C_s L_s}} \quad (4.1)$$

And parallel resonance radical frequency,

$$\omega_p = \frac{1}{\sqrt{L_s \frac{C_0 C_s}{C_0 + C_s}}} \quad (4.2)$$

4.1.2 Electrical Impedance Matching Methodologies

There are various methods available for achieving impedance matching between the driving electronics and the transducer, such as using matching networks, considering the material properties of the transducer, optimizing the transducer design, and adjusting the cable length. In certain instances, the selection of the diameter of the PZT element [30], and cable length [31] is made for impedance-matching purposes. The use of multilayer transducers has been reported to enhance both the signal-to-noise ratio and the amount of energy that is transmitted [32]. Focused array transducers are made via a technique using the multilayer lamination of polyurethane (PU) thin films to increase the capacitance and achieve electrical impedance matching [33]. Some studies focused on modifying the volume ratio to adjust the dielectric constant for PVDF-based materials to achieve impedance matching [34]. Modified ceramic with larger permittivity was used in some studies [35]. The purpose of these modifications was to create transducers with electrical impedance that are compatible with the system.

Regarding impedance-matching networks, traditional ones contain various components such as capacitors, inductors, transformers, and transmission lines. Among the various types of networks, L-networks contain a combination of inductors and capacitors, hence providing several benefits like convenient tuning, cost-effectiveness, and high accuracy [4], [11], [36]. After the determination of the transducer's frequency which is influenced by factors such as its material, configuration, and intended use, the design topology and values of the matching

network components can be undertaken. Subsequently, the EIMNs can be integrated into a printed circuit board (PCB). The majority of EIMNs feature fixed topologies and have been specifically designed to accommodate a specific transducer that operates near its resonance frequency. In certain instances where an EIMN needs to work together with unknown transducers or when there is significant variation in transducer impedance during operation, the effectiveness of the ultrasonic system may be impaired, resulting in unpredictable results [36], [37]. Furthermore, the characteristics of the IMNs must be adaptable to provide dynamic matching for varying working situations. In addition to those considerations, the network would be favoured if it demonstrates efficacy across a broad range of frequencies. Different broadband IMN techniques have been implemented for ultrasound imaging purposes to acquire wide bandwidth signals for enhanced axial resolution [21], [23]–[26]. However, broadband integrated microwave networks (IMNs) typically exhibit frequency responses that are reasonably consistent and may not be suitable for applications that require high-power.

4.2 Aims and objectives

The overall aim of this work presented in this chapter was to design and build a novel programmable/dynamic matching network for therapeutic ultrasound transducers for an efficient therapy such as drug delivery. This chapter provides an overview of models, and electrical properties that are commonly used in electrical matching. It also discusses the many approaches that can be used for designing Electrical impedance-matching networks. Additionally, it introduces a new programmable single EIMN that is capable of supporting multiple frequencies for different transducers for matching purposes. This allowed us to excite transducers with their 3rd and 5th harmonics from a single matching network. The dynamic matching network's performance was tested with 2 different transducers for different frequencies.

4.3 Materials and methods

Designing an impedance matching network could be divided into three main steps: (1) measuring the transducer's complex impedance, (2) designing the right matching configuration based on a simulation or calculation, and (3) testing the designed matching network experimentally.

4.3.1 Complex impedance measurements of ultrasound transducers

Before designing a matching network, it is important to measure the impedance of the transducer. To determine the impedance of a transducer, it is necessary to measure a minimum of two values (voltage and current), as impedance is a complex quantity. Contemporary impedance measuring devices such as Impedance analysers (IA), and vector network analysers (VNA) typically assess both the real and imaginary components of an impedance vector, subsequently transforming them into specific characteristics such as magnitude $|Z|$, phase (θ), admittance magnitude $|Y|$, resistance (R), reactance (X), conductance (G), susceptance (B), or capacitance (C), and inductance (L). There are also other equipment or methods that have been explored in studies to measure the impedance of a transducer rather than using VNAs [37]–[39]. The electric impedance of commercially available 0.5 MHz (Olympus, Tokyo, Japan) and 1 MHz (Olympus, Tokyo, Japan) transducers used in our experiments was measured by an impedance analyser (4395A Network/Impedance Analyzer, Agilent Technologies, Santa Clara, California, USA) (Table 4.1).

Table 4.1. Measured impedance values for two different transducers at 3 different frequencies.

	Frequency	Impedance $ Z $	Resistance (R)	Reactance (X)	Phase angle (θ)
1 MHz Transducer	1 MHz	153.36 Ω	147.16 Ω	24.407 Ω	10.33°
	3 MHz	20.57 Ω	10.29 Ω	-17.79 Ω	-59.75°
	5 MHz	4.11 Ω	3.38 Ω	-2.34 Ω	-34.50°
0.5 MHz Transducer	0.5 MHz	105.32 Ω	92.30 Ω	-50.45 Ω	-28.56°
	1.5 MHz	35.48 Ω	6.39 Ω	-34.92 Ω	-79.607°
	2.5 MHz	20.00 Ω	3.06 Ω	-19.77 Ω	-81.184°

4.3.2 Designing a programmable/dynamic matching network

The Smith chart can be used to construct a matching circuit topology to align a transducer's input impedance with the driving electronics' output impedance. The L-type matching network was chosen due to its simplicity, and broad range of coverage across the Smith chart. Overall, eight different topologies could be created by using inductors and capacitors in L-type configurations. By altering the switches in which series-added inductors and parallel-

added capacitors are mounted, it is possible to achieve four L-type topologies that can cover the entire Smith chart (Figure 4.3.). After the impedance measurements of transducers from the Impedance Analyzer, we calculated individual L-type matching networks for transducers' fundamental frequencies and 3rd and 5th harmonic frequencies. We also used an online tool [40] to find out the best matching topologies for different frequencies.

We used MP4835A (Monolithic Power Systems (MPS), Kirkland, Washington, USA), a 32-channel high-voltage ($\pm 100V$) switch to allow adding inductors in series or capacitors in parallel to allow dynamic range of values in inductors and capacitors. Switches are controlled by a 32-bit data latch from Teensy 4.1 microcontroller (PJRC, Sherwood, OR). A total of five MP4835A chips were used in our dynamic matching network, which allowed 4 different types of L-networks with a final inductor value ranging from 1 nH to 199.999 μH with a 1nH sensitivity, and a final capacitor value ranging from 1 pF to 99.999 nF with a 1 pF sensitivity (Figure 4.5). The programmable matching network was integrated into a PCB sized 25 cm x 15 cm (Figure 4.4).

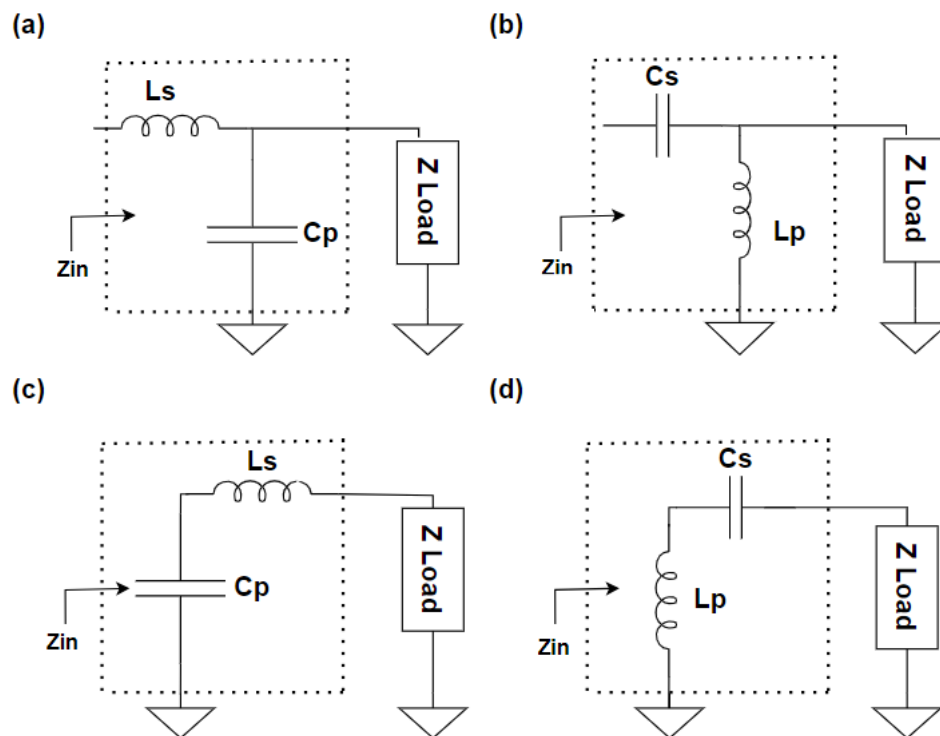


Figure 4.3. Four different configurations for L-type impedance matching networks were used to cover the entire Smith chart. If the electrical impedance of the driving electronics is smaller than transducer type(a) and type (b), larger than transducer type (c) and type (d) are used.



Figure 4.4. Design of a programmable matching network on a PCB.

The list of the pins connected in switches was defined and a function was created in MATLAB. The required switches are turned on based on the required configuration (type a, b, c, d) and the value of inductor and capacitor which is calculated for a specific frequency for a specific transducer. The command which contains the information about the on/off status of switches was sent via serial interface to Teensy 4.1 microcontroller. Each time this was repeated for different settings such as different topologies and different values.

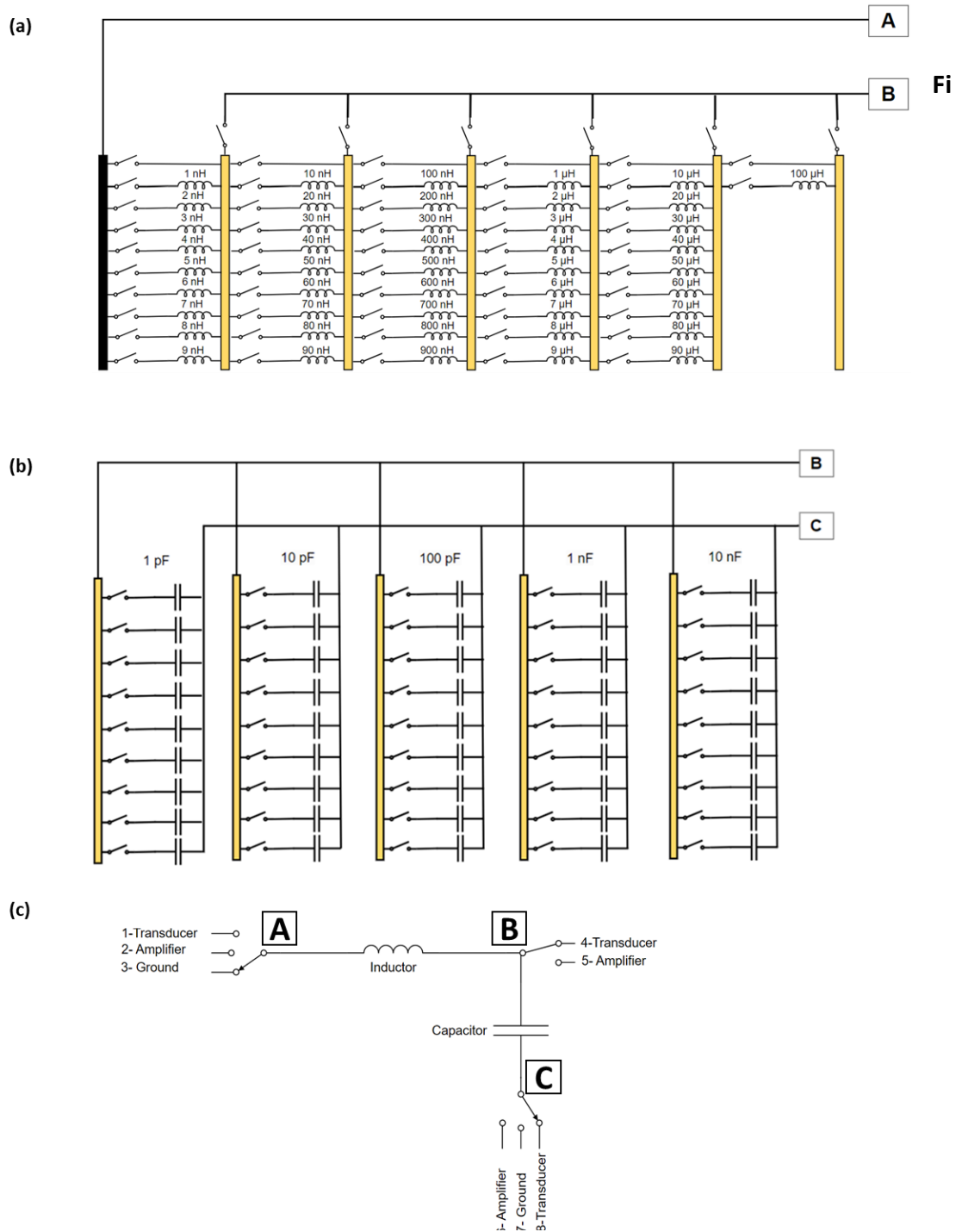


Figure 4.5. The overall structure of the dynamic matching network (c) creates different types of L-networks by adding inductors in series (a) and capacitors in parallel (b) via programmable switches. Capacitors ranging from 1 pF to 10nF connected in parallel with switches allowing a final capacitor value ranging from 1 pF to 99.999 nF with a 1 pF sensitivity (b). Inductor values ranging from 1 nH to 100 μ connected in series to create a final inductor value ranging from 1 nH to 199.999 μH (a).

4.3.3 Experimental Setup for testing the dynamic matching network

Transducers were placed in a water tank which filled with degassed and deionised water. The transducers (1 MHz and 0.5 MHz) were excited by a function generator (33500B series, Agilent Technologies, Inc., Wood Dale, IL, USA) through an RF power amplifier (50 dB, 2100L, Electronics & Innovation Ltd., Rochester, NY, USA). A dynamic matching network was connected between each transducer and the amplifier. Each transducer was excited with 10 cycles with and without a matching network connected. Different configurations of L-type matching were applied for each transducer for its own 1st, 3rd, and 5th harmonic frequencies. The signals were received by a 1mm needle hydrophone (Precision Acoustics, Dorchester, U.K.) were amplified by a commercial amplifier (gain:25, SIM914, Stanford Research Systems, Sunnyvale, CA, USA) and then digitized by a GaGe digitizer (Octave 14, Dynamic Signals, San Bruno, CA, USA) and recorded by a computer (Figure 4.6).

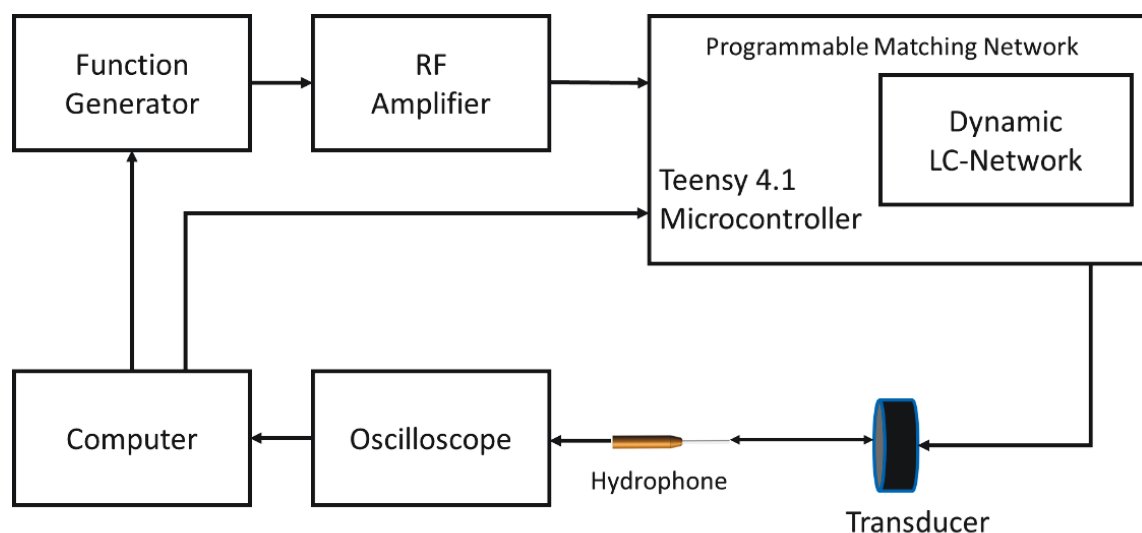


Figure 4.6. Experimental setup for evaluating the performance of the dynamic matching network. The 1 mm hydrophone was placed against the transducer at each transducer's focal point. The programmable/dynamic matching network was connected between the RF amplifier and the transducer. The signals were digitized by an oscilloscope and stored on a computer.

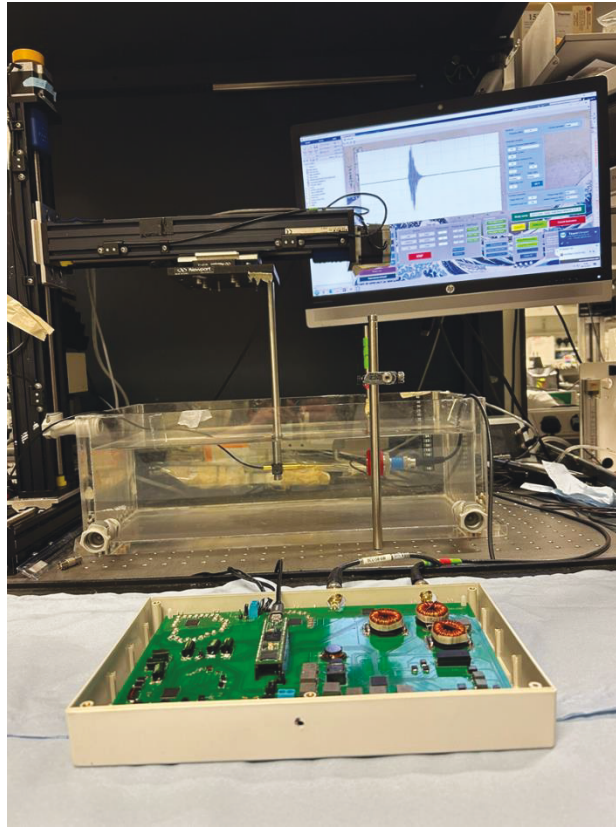


Figure 4.7. The photograph of designed and constructed programmable matching network in an experimental setup.

4.4 Results

4.4.1 Different transducers' fundamental frequency matching

We tested first the fundamental frequency matching capabilities of our dynamic matching design for different transducers. For the 0.5 MHz Olympus transducer, we tested all 4 different L-type topologies. Then we also tested with another topology which contained an inductor connected in series with a transducer, and finally tested without a matching network connected (Figure 4.8). The time domain signals demonstrated that type-b matching performed better than other configurations. It increased the Peak-Negative-Pressure (PNP) by 89.8 % compared to no matching network-connected results (Figure 4.8 (g)). Fast-Fourier-Transform (FFT) was performed to evaluate the matching network on transducer frequency.

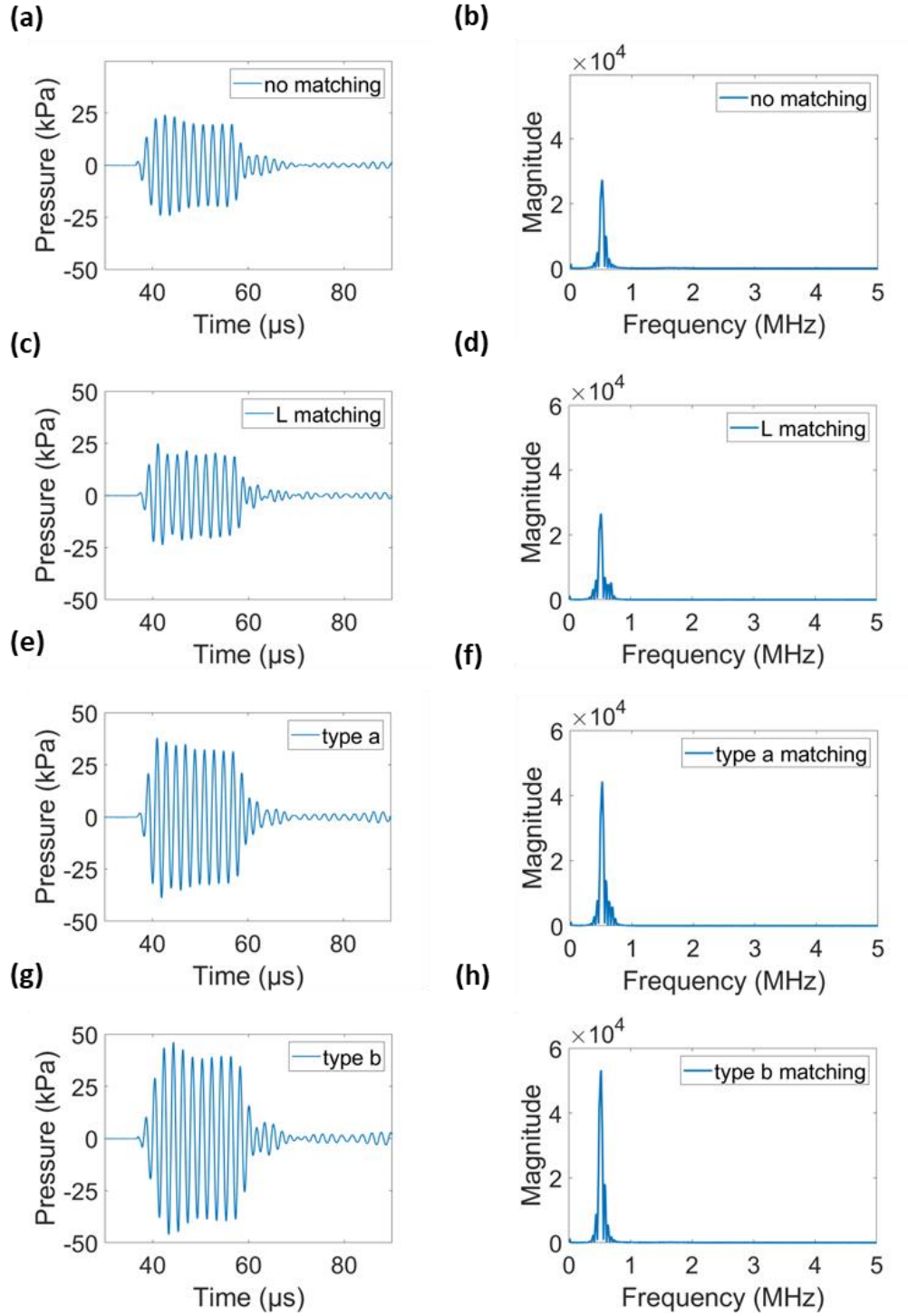


Figure 4.8. Fundamental frequency matching for 0.5 MHz transducer. Different matching configurations were tested with the transducer's fundamental frequency with 10 cycles. Signals were captured by a 1mm needle hydrophone. The time domain signals for no matching (a), series inductor (c), type-a matching (e), and type-b matching (g). The frequency spectrum for no matching (b), series inductor (d), type-a matching (f), and type-b matching (h).

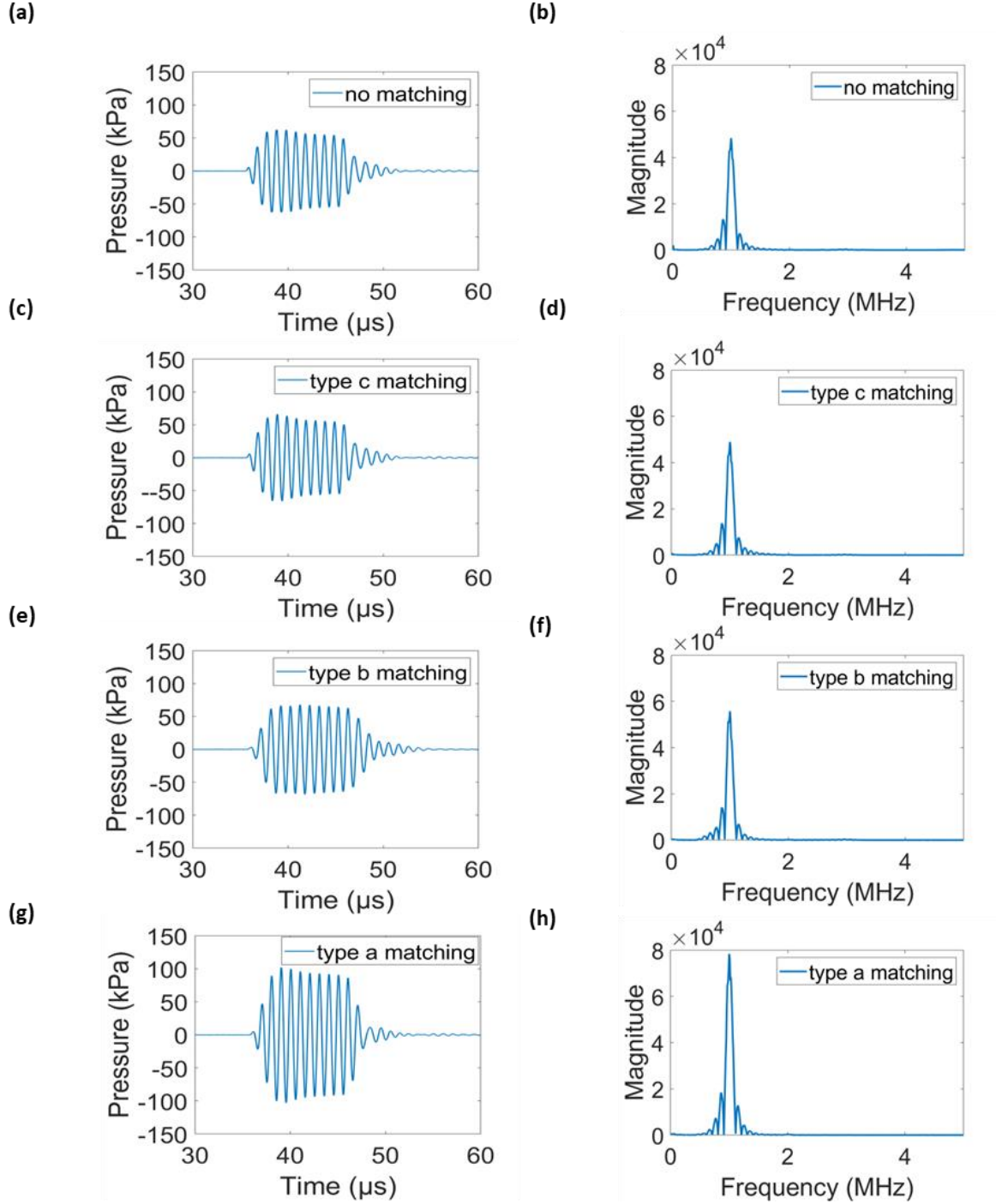


Figure 4.9. Fundamental frequency matching for 1 MHz transducer. Different matching configurations were tested with the transducer's fundamental frequency with 10 cycles. Signals were captured by a 1mm needle hydrophone. The time domain signals for no matching (a), type-c matching (c), type-b matching (e), and type-a matching (g). The frequency spectrum for no matching (b), type-c matching (d), type-b matching (f), and type-a matching (h).

We tested the second transducer which is 1 MHz Olympus transducer with $153.36\ \Omega$ impedance with all 4 different L-type topologies. Then we also tested with another topology which contained an inductor connected in series with a transducer, and finally without a matching network connected (Figure 4.9). As the transducer's impedance is larger than the amplifier's output impedance, therefore type-a and type-b matching should perform better than other types of matching. The time domain signals demonstrated that type-a matching performed better than other configurations. It increased the Peak-Negative-Pressure (PNP) by 66 % compared to no matching network-connected results (Figure 4.8 (g)). Fast-Fourier-Transform (FFT) was performed to evaluate the matching network on the transducer's frequency.

4.4.2 Harmonic frequency matching of a single transducer

The second part of our experiments was performed harmonic frequency matching for a 1 MHz transducer. We excited the 1 MHz transducer with 10 cycles at its 3rd (3 MHz) and 5th (5 MHz) harmonics in an experimental setup same as before.

For the 3rd harmonic excitation, the transducer's impedance was measured as $20.57\ \Omega$ which was smaller than the amplifier's output impedance, so we expected that type-c and type-d matching should be performed better than other types of matching. As we expected, type type-d matching performed a lot better than other types of matching. It improved the output voltage by 422.52 % more than no matching output (Figure 4.10 (g)). However, type-b and type-c matching outputs were almost identical. They improved the output voltage by around 260 % compared to no-matching output (Figure 4.10 (c), (e)).

For the 5th harmonic excitation, the transducer's impedance was measured as $4.11\ \Omega$ which was a lot smaller than the amplifier's output impedance, so again we expected that type-c and type-d matching should be performed better than other types of matching. As we expected, type type-c matching performed a lot better than type-a and series inductor matching. It improved the output voltage by 239.2% more than no matching output (Figure 4.11 (b)). However, type-b matching performed the best compared to other topologies even though this configuration was used commonly for matching the smaller impedance to the larger impedance. Type-b matching configuration improved the output voltage by around 243.2 % compared to no-matching output.

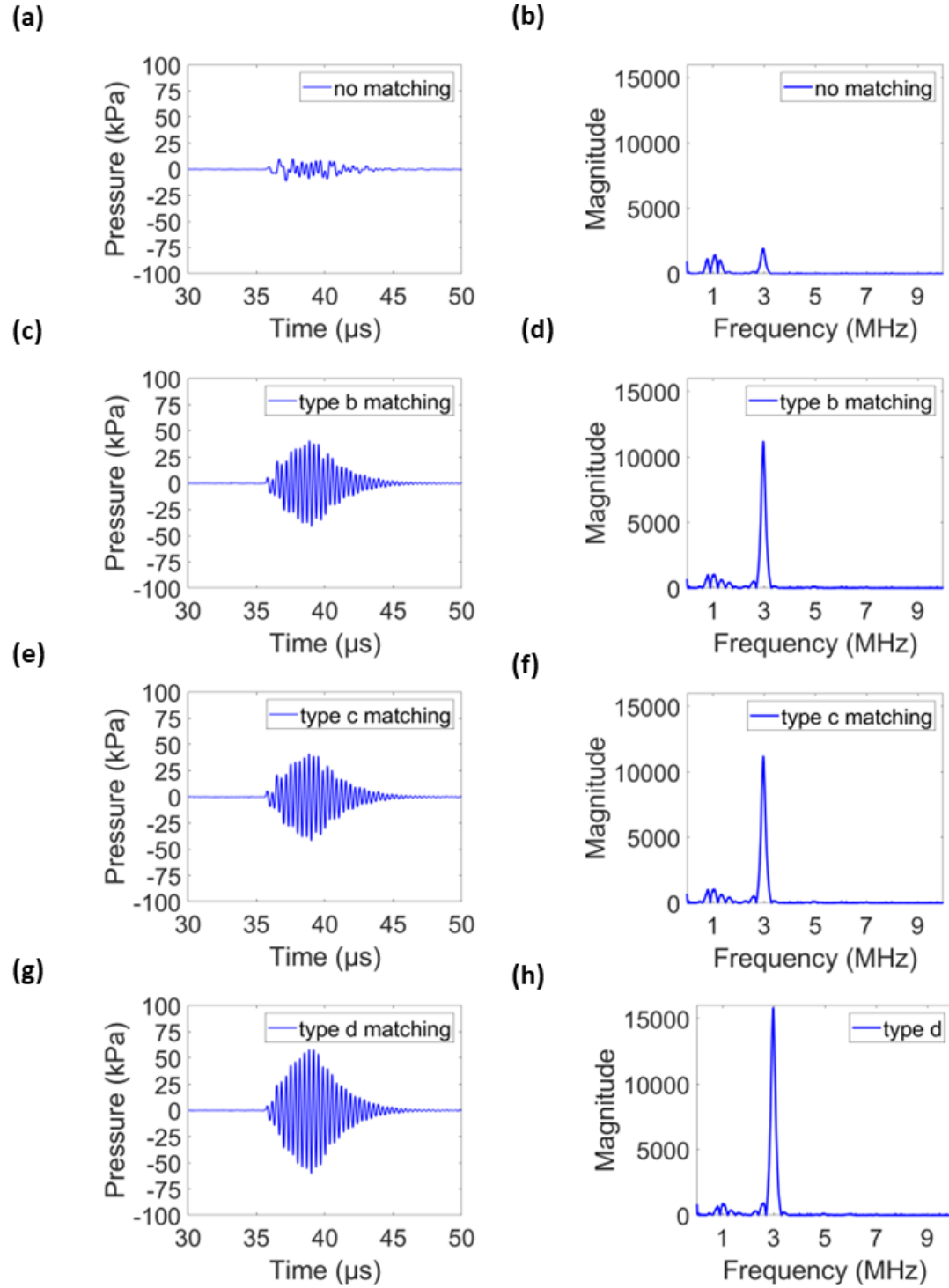


Figure 4.10. 3rd harmonic frequency matching for 1 MHz transducer. Different matching configurations were tested with the transducer's 3rd harmonic frequency with 10 cycles. Signals were captured by a 1mm needle hydrophone. The time domain signals for no matching (a), type-b matching (c), type-c matching (e), and type-d matching (g). The frequency spectrum for no matching (b), type-b matching (d), type-c matching (f), and type-d matching (h).

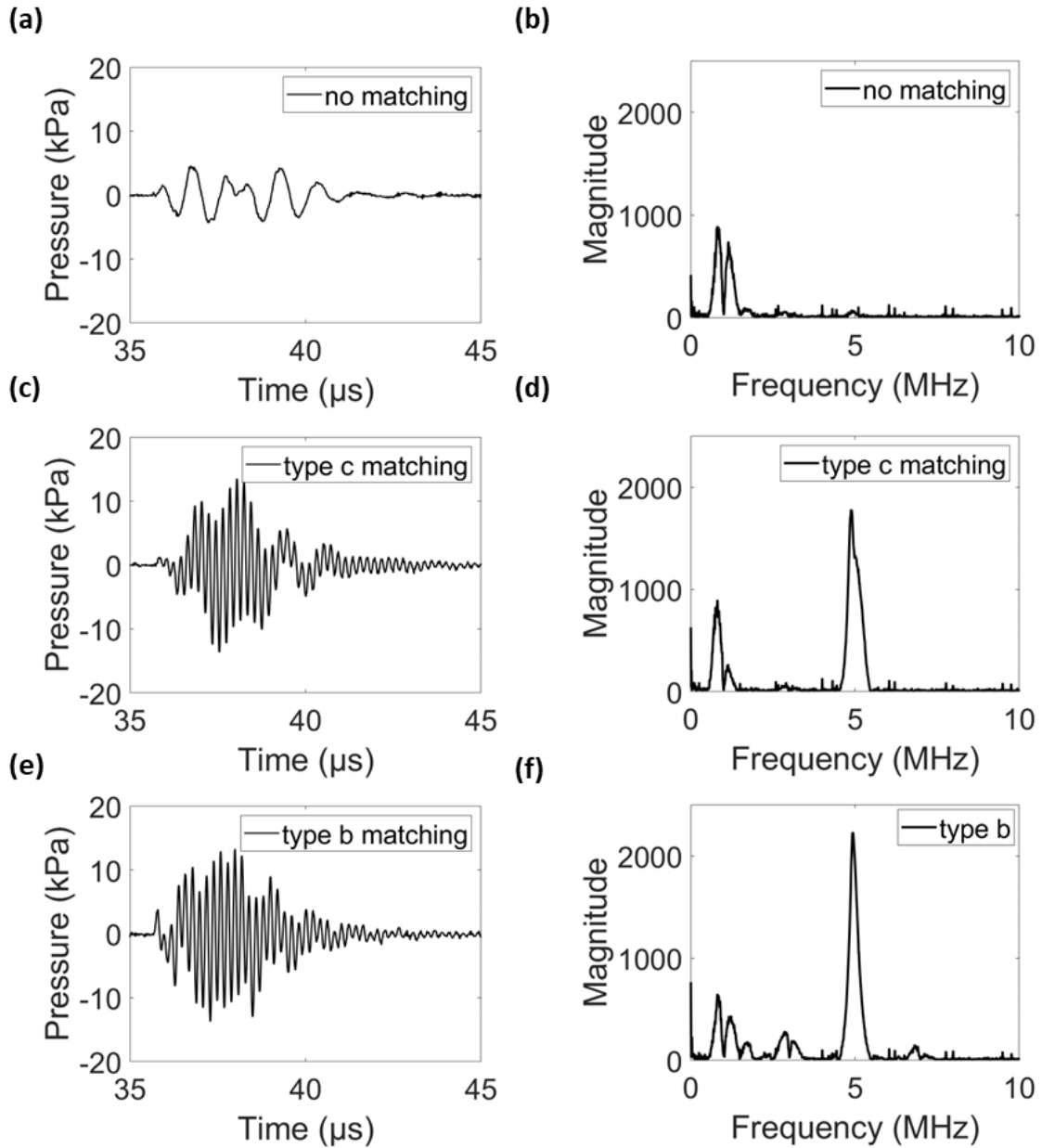


Figure 4.11. 5th harmonic frequency matching for 1 MHz transducer. Different matching configurations were tested with the transducer's 5th harmonic frequency with 10 cycles. Signals were captured by a 1mm needle hydrophone. The time domain signals for no matching (a), type-c matching (c), and type-b matching. The frequency spectrum for no matching (b), type-c matching (d), and type-d matching (f).

4.5 Discussion

The impedance mismatch between transducers and connected electronics, such as amplifiers, can lead to energy reflection, excessive energy consumption, and potential damage to electronic components. Traditional impedance matching networks, while effective in narrowband applications, face limitations when dealing with broadband or multi-frequency requirements. The presented work in this chapter bridges this gap by proposing a dynamic matching network that can adapt to different transducers and frequencies. L-type matching networks perform well in a narrow bandwidth because of their design components' frequency dependencies. When we combined this performance with our dynamic configuration, we were able to design a broadband matching network without sacrificing its performance. The current prototype of our dynamic matching network has a wide range of matching capabilities owing to the number of inductors and capacitors used which could be improved even more by adding more capacitors and inductors. The dynamic matching network was able to match two different transducers at their fundamental frequencies. Even though we were able to increase the output pressure by using our design, we could potentially improve the output even better. Values of inductors and capacitors were calculated based on an online tool and configuration, but errors could be introduced to our design due to the difference between the actual values of the components and their nominal values. Additionally, the impedance of transducers was measured via an Impedance Analyzer which is under low voltage and current. This could be different in actual experiments which require high voltage and current. Our design has a maximum voltage limitation of $\pm 100\text{V}$ due to the IMP4835A 32-channel switch's limitation. The matching capabilities of our design were only tested for emission purposes. Reception matching was not tested.

Our current design was implemented in a way that requires impedance measurements before deciding the matching topology, but this could be eliminated if we combine our design with a real-time measurement method such as the voltage/ current reading method [41] or phase-difference method [42]. We could also design a transducer calibration system that can try every possible network topology and excite and capture the signals via a needle hydrophone. Based on the maximized pressure it can decide the right topology for different transducers and different frequencies. MATLAB commands controlled our current matching

network design, switching between different topologies and values of inductors and capacitors. An algorithm can excite a transducer, switch between different topologies and values, and capture the PNP for each case. After completing all of the combinations and finding the PNP values, it can stay at the highest-pressure topology and values. This approach eliminates the need for prior impedance knowledge of transducers and eliminates the need for expensive vector analysers. Additionally, with this approach there will be no need for external voltage/current probes [41-42] and can be used as an impedance calibration system combined with the transducer calibration.

Our design is successfully matching various frequencies for different transducers. For 1 MHz transducer, 5th harmonic frequency excitation demonstrated in the frequency spectrum, without a matching network transducer itself was not efficient, but with a matching network the output pressure improved around 243.2 %. In figure 4.11, type B matching (for the 5th harmonic matching), secondary peaks are minimized but not completely eliminated. These peaks indicate areas where the matching network could potentially be further optimized to achieve even better performance. The presence of a dominant peak at the target frequency with minimal other harmonic content is indicative of optimal matching, crucial for effective and safe therapeutic ultrasound applications.

4.6 Conclusion

The presented work in this chapter addresses the important challenge of designing a programmable and dynamic matching network for therapeutic ultrasound transducers, focusing on applications such as drug delivery. The significance of this research lies in its potential to enhance the efficiency of therapeutic ultrasound systems while providing a cost-effective alternative for matching networks used with multiple transducers across a broader range of frequencies. A multi-transducer and multi-frequency programmable matching network were designed and constructed, followed by an evaluation of its acoustic performance with two different transducers. Experimental results demonstrate the effectiveness of our dynamic matching network in improving the Peak-Negative-Pressure for both transducers at their fundamental frequencies. The fundamental frequency matching as well as harmonic frequency matching for a 1 MHz transducer at its 3rd and 5th harmonics was also evaluated. More than a 200 % increase at the PNP was observed for both harmonic

frequency matching. The dynamic matching network shows promise in achieving efficient impedance matching for diverse frequencies and transducers.

4.7 References

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5 Conclusion and future outlook

The BBB is a physical, transport, and enzymatic barrier between the bloodstream and the extracellular fluid of the central nervous system (CNS). The current treatment options for brain diseases have limited efficacy, mostly attributable to the presence of a blood-brain barrier (BBB). Studies have demonstrated that focused ultrasound in conjunction with microbubbles can temporarily disrupt the BBB, enabling brain drug delivery. A study using short-pulse ultrasound therapy showed that it could deliver drugs across the blood-brain barrier (BBB) more reliably while reducing the risk of tissue damage. Currently, there are no specifically engineered devices for generating short-pulse ultrasound. However, most commercially available multi-channel arrays and their drivers were designed for imaging or thermal ablation, so they are either not suitable or too expensive for other therapeutic applications, such as microbubble-based methods. In this thesis, an ultrasound driver that is suitable for low-intensity microbubble-based therapeutic ultrasound applications was designed and was tested its short-pulse emitting performance. Then our design was extended to 8-channel and 16-channel drivers based on the single-channel driver design. The acoustic performance of multi-channel drivers in water was tested. Finally, a dynamic matching network was designed to improve the effectiveness of therapeutic ultrasound systems while offering a cost-efficient option for matching networks implemented with multiple frequencies.

A cost-effective and simple single-channel driver in Chapter 2 that efficiently drives arrays with a large number of elements was designed. The driver generates a square wave and passes it through a matching network to produce a sinusoidal waveform. Two digital signals with a voltage range of 0-3.3V from a microcontroller controlled the amplitude and frequency of the single-channel driver. The single-channel driver demonstrated tunability in the frequency range of 0.1–1 MHz and the ability to generate short pulses with amplitudes ranging from 0-150 V. The high-voltage T/R switch in our design allows low-voltage microbubble signal reception without the requirement of external supplies or external control signals.

In Chapter 3, two multi-channel array drivers were designed, namely an 8-channel driver and a 16-channel driver. Their acoustic performances were characterised, and their abilities at steering and focusing an ultrasound beam in water were tested. The performances of both

multi-channel drivers were evaluated by independently testing each channel using a single transducer to observe the differences between channels. The implementation of a modular assembly architecture allowed for easy repair and replacement of individual components, hence improving the simplicity and cost-effectiveness of arrays and drivers' maintenance. A randomization technique was implemented to improve the performance of element arrangement in the arrays. Systems for ultrasound-mediated therapies must meet certain design specifications to improve treatment efficacy and safety. These include a large number of channels, the output of sub-megahertz frequencies, and, potentially, short ultrasound pulses. Existing multi-channel driver systems either cannot satisfy all of these requirements or are too expensive due to the inclusion of features for imaging applications. Therefore, a low-cost, highly scalable, multi-channel driver system was developed. The overall cost of a 128-channel driver circuit was estimated, excluding the power supply and the control unit, to less than \$1600. For prototyping purposes Bench type power supplies were used but the final design can be equipped with a single compact/cheap power supply unit for 150V DC. When combined with recently developed rapid 3D prototyping methods for making ultrasound transducers, our low-cost circuit could facilitate making therapeutic ultrasound array technologies more widely accessible and ubiquitous.

In Chapter 4, the critical importance of designing effective electrical impedance-matching networks for piezoelectric transducers used in ultrasound therapy was investigated. This study is important because it has the potential to improve the performance of therapeutic ultrasound systems and provide a cost-effective solution for matching networks used with multiple transducers and frequency ranges. A programmable matching network that can support several transducers and frequencies was designed. The acoustic performance of the system using two separate transducers was assessed. The test results show that our dynamic matching network does a good job of raising the peak negative pressure for both transducers at their fundamental frequencies. The dynamic matching network for harmonic frequency matching from the same transducer was also tested. A significant increase of over 200% in the PNP for each harmonic frequency (3rd and 5th) was observed compared to the output pressure without matching. The dynamic matching network demonstrates remarkable versatility and adaptability, highlighting its potential to enhance transducer performance across diverse applications and frequency ranges. Continued refinement and validation of

the proposed methodology could pave the way for substantial advancements in the design and optimisation of piezoelectric devices.

In conclusion, this thesis has made a significant contribution by designing and constructing a multi-channel driver for short-pulse ultrasound therapy and improving the transmission and reception efficacy via matching networks. Our multi-channel driver, coupled with an array, can effectively and affordably function as a device for therapeutic ultrasound arrays with higher element counts, as demonstrated by this research. Additionally, our dynamic matching network offers a cost-efficient option for matching networks implemented with multiple frequencies. For future work, our drivers' output pressure could be improved by lowering individual channels' output impedances. This will lead to a reduction in the overall required channel numbers, hence the overall cost of the design. Our multi-channel driver system was built with high-voltage T/R switches, so with a custom-made data-acquisition system, it can allow the reception of acoustic signals generated by microbubbles. This can allow safe and localised real-time drug delivery monitoring. Additionally, our dynamic matching network could be combined with a transducer calibration system which contains a needle hydrophone for receiving acoustic pressure. This will allow real-time monitoring of the output pressure of a transducer which is connected with different types of matching networks with different component values. With an algorithm, the maximized pressure and the required network with component values can be found. By creating such a system, the requirement of expensive measurement tools (Impedance Analysers, Vector Analysers etc.) could be avoided.

6 Appendix

Chapter 3: Control Unit Codes

Master Controller

```
master_f_control_prog | Arduino IDE 2.2.1
File Edit Sketch Tools Help

Teensy 4.1

master_f_control_prog.ino
1 // ----- //
2 #define debugmode 0
3 #define a_control_slave_address 17
4 //
5 //error codes
6 //input format:
7 //[command]:[ch]:[val]
8 //-1 missing first colon
9 //-2 missing second colon
10 //-9 command not recognised
11 // ----- //
12
13
14
15 //R Gemmell Teensy 4 I2C lib:
16 #include <i2c_device.h>
17 #include <i2c_driver.h>
18 #include <i2c_driver_wire.h>
19 #include <i2c_register_slave.h>
20
21 // #include <Wire.h>
22 #define boardLED 13
23 #define triggerout 20
24 // reserve pin 18 19 for I2C communication
25
26
27 // serial communication with a pc
28 String commandin_string; // for command input
29 unsigned int byteout[4], valin; // input 4 bytes = 1x int32
30 char commandout_chararray[10];
31 unsigned int i;
32 String serialin;
33 String thiscommand;
34 String target_address_string;
35 int target_address;
36 uint32_t thiscommandvalue;
```

master_f_control_prog | Arduino IDE 2.2.1

File Edit Sketch Tools Help

Teensy 4.1

master_f_control_prog.ino

```
35 int target_address;
36 uint32_t thiscommandvalue;
37 int markidx, markidx2;
38 String thiscommandvalue_string;
39 char thiscommandvalue_char[] = "";
40 String translated_command;
41 boolean a_control;
42
43 void setup() {
44     pinMode(boardLED, OUTPUT);
45     pinMode(triggerout, INPUT); // external trigger mode
46     digitalWrite(boardLED, LOW);
47     digitalWrite(triggerout, LOW);
48     Wire.begin(); // join i2c bus (address optional for master)
49
50     Serial.begin(9600);
51     Serial.flush();
52 }
53
54 void loop() {
55
56     // ----- Read incoming serial command -----
57     if (Serial.available() <= 0) { // no incoming command
58     }
59     else { // incoming command detected
60         if (debugmode) {
61             Serial.println("detected incoming command -- reading ...");
62         }
63         serialin = Serial.readString();
64         serialin.trim();
65         if (serialin.equalsIgnoreCase("*")) { //trigger
66             if (debugmode) {
67                 Serial.println("sending trigger");
68             }
69             digitalWrite(boardLED, HIGH);
70             digitalWrite(triggerout, HIGH);
71             delay(10);
72             digitalWrite(boardLED, LOW);
73             digitalWrite(triggerout, LOW);
74         }
75         else {
76
77             // ----- Command format -----
78             if (debugmode) {
79                 //Serial.println("scanning for colon mark ...");
80             }
81         }
82     }
```

```

master_f_control_prog | Arduino IDE 2.2.1
File Edit Sketch Tools Help

Teensy 4.1

master_f_control_prog.ino

82     }
83
84     markidx = serialin.indexOf(':');
85     if (markidx >= 30 || markidx < 0) {
86         markidx = -1; // no ':' found in the serial stream input
87         if (debugmode) {
88             Serial.println("input format should be command:channel:value\n");
89         }
90
91         Serial.flush();
92         Serial.println(-1); // print error code
93
94     }
95     else { // good command format
96         if (debugmode) {
97             //Serial.println("no error (code 0) -- colon found");
98             //Serial.println(markidx);
99         }
100
101         commandin_string = serialin.substring(0, markidx);
102         target_address_string = (serialin.substring(markidx + 1));
103
104         // find another colon separating address and value
105         markidx2 = target_address_string.indexOf(':');
106         //Serial.println(target_address_string);
107         //Serial.println(markidx2);
108         if (markidx2 < 0) {
109             if (debugmode) {
110                 Serial.println("needs colon separating address and value\n");
111             }
112             Serial.println(-2); // print error code
113         }
114         else {
115             thiscommandvalue_string = (target_address_string.substring(markidx2 + 1));
116             target_address_string = (target_address_string.substring(0, markidx2));
117
118             target_address_string = (target_address_string.substring(0, markidx2));
119
120             target_address = target_address_string.toInt();
121             thiscommandvalue = thiscommandvalue_string.toInt();
122
123             if (debugmode) {
124                 //Serial.print("command value length :: ");
125                 //Serial.println(thiscommandvalue_string.length() - 1);
126                 Serial.print(":: command :: ");
127                 Serial.println(commandin_string);
128                 Serial.print(":: target :: ");
129                 Serial.println(target_address);
130                 Serial.print(":: val :: ");
131                 Serial.println(thiscommandvalue);
132             }
133             Serial.flush();
134
135
136             // ----- Command interpretation -----
137

```

master_f_control_prog.ino

```
137
138 // transmission sequence
139 translated_command = translate(commandin_string);
140 if (!translated_command.equals("0")) { // string translate(string) returns '0' if the command is not recognise
141     translated_command.toCharArray(commandout_chararray, translated_command.length() + 1);
142
143     if (a_control) {
144         transmit_a_control(target_address, commandout_chararray, thiscommandvalue);
145     }
146     else {
147         transmit_f_control(target_address, commandout_chararray, thiscommandvalue);
148     }
149     Serial.println(0);
150     if (debugmode) {
151         Serial.println(":: Valid command :: sent the following thru I2C ::");
152         Serial.print(target_address);
153         Serial.print(commandout_chararray);
154         Serial.println(thiscommandvalue);
155     }
156 }
157
158
159
160 else { // unrecognised command
161     Serial.println(-9);
162     if (debugmode) {
163         Serial.println("command not recognised -- not sending this to a slave. The command is");
164         Serial.println(commandin_string);
165         Serial.println("expected :: frq freq frequency / cyc cycles cycles / dly delay / onf onoff io");
166     }
167 }
168 }
169 }
170 }
171 }
172 }
```

```
173
174 void transmit_a_control(int channeltoiset, char commandout[], uint32_t valout) {
175     digitalWrite(boardLED, HIGH); // briefly flash the LED
176
177     byteout[3] = (valout) & 0xFF;
178     byteout[2] = (valout >> 8) & 0xFF;
179     byteout[1] = (valout >> 16) & 0xFF;
180     byteout[0] = (valout >> 24) & 0xFF;
181
182
183     Wire.beginTransaction(a_control_slave_address); // transmit to device
184     Wire.write(commandout); // sends command -- f-control boards will only use first 3 chars (4 bytes)
185     Wire.write(channeltoiset);
186     Wire.write(byteout[0]); // send 4 bytes int (32 bits)
187     Wire.write(byteout[1]);
188     Wire.write(byteout[2]);
189     Wire.write(byteout[3]);
190     Wire.endTransmission(); // stop transmitting
191
192     digitalWrite(boardLED, LOW);
193     if (debugmode) {
194         Serial.println(":: sent amplitude control signal ::");
195         Serial.print(commandout); // sends command -- f-control boards will only use first 3 chars (4 bytes)
196         Serial.print(channeltoiset);
197         Serial.print(">>");
198         Serial.println(valout);
199     }
200 }
201
202 void transmit_f_control(int slave_address, char commandout[], uint32_t valout) {
203     digitalWrite(boardLED, HIGH); // briefly flash the LED
204
205     byteout[3] = (valout) & 0xFF;
206     byteout[2] = (valout >> 8) & 0xFF;
207     byteout[1] = (valout >> 16) & 0xFF;
208     byteout[0] = (valout >> 24) & 0xFF;
```

```

master_1_control_prog.ino
209
210
211 Wire.beginTransmission(slave_address); // transmit to device
212 Wire.write(commandout); // sends command -- f-control boards will only use first 3 chars (4 bytes)
213 Wire.write(byteout[0]); // send 4 bytes int (32 bits)
214 Wire.write(byteout[1]);
215 Wire.write(byteout[2]);
216 Wire.write(byteout[3]);
217 Wire.endTransmission(); // stop transmitting
218
219 digitalWrite(boardLED, LOW);
220 if (debugmode) {
221   Serial.println(":: sent frequency control signal ::");
222   Serial.print(commandout); // sends command -- f-control boards will only use first 3 chars (4 bytes)
223   //Serial.print(channeltoreset);
224   Serial.print(">>");
225   Serial.println(valout);
226 }
227 }
228
229 String translate(String stringin) {
230   // char translate(string) returns '0' if the command is not recognise
231   String stringout; //output command for slave teensys
232
233   a_control = false; //change to true for some if conditions
234   // frequency control commands
235   if (stringin.equalsIgnoreCase("frq") || stringin.equalsIgnoreCase("freq") || stringin.equalsIgnoreCase("frequency")) {
236     stringout = "frq";
237   }
238   else if (stringin.equalsIgnoreCase("dly") || stringin.equalsIgnoreCase("delay")) {
239     stringout = "dly";
240   }
241   else if (stringin.equalsIgnoreCase("cyc") || stringin.equalsIgnoreCase("cycle") || stringin.equalsIgnoreCase("cycles")) {
242     stringout = "cyc";
243   }
244
245   n.equalsIgnoreCase("io") || stringin.equalsIgnoreCase("onf") || stringin.equalsIgnoreCase("onoff")) {
246     nf";
247
248
249   trol commands
250   n.equalsIgnoreCase("tarf") || stringin.equalsIgnoreCase("tarf") || stringin.equalsIgnoreCase("targetf") || stringin.equalsIgnoreCase("targf") || stringin.equalsIgnoreCase("targetfrequency")) {
251     af";
252     ue;
253
254   n.equalsIgnoreCase("dc") || stringin.equalsIgnoreCase("dutydcycle") || stringin.equalsIgnoreCase("dcy")) {
255     cy";
256     ue;
257
258
259
260
261   cognise command
262   ";
263
264   ;
265
266
267

```

Slave Boards for Amplitude Control:



```
1 // ----- //
2 #define myid 17
3 #define serialdebugmode 0
4 #define half_led_blink_period_ms 150
5 #define num_channels 8
6 #define default_dc 50
7 #define dc_adjust_resolution 1000
8 #define loops_per_us 7.3
9 // ----- //
10
11
12 //R Gemmell Teensy 4 I2C lib:
13 #include <i2c_device.h>
14 #include <i2c_driver.h>
15 #include <i2c_driver_wire.h>
16 #include <i2c_register_slave.h>
17
18 // #include <Wire.h>
19 #define boardLED 11
20 #define redLED 13
21 int output_ch[num_channels+1] = {4, 33, 34, 35, 36, 3, 2, 1, 0};
22
23 //emission variables
24 uint32_t targetf = 10000;
25 uint32_t num_ticks = (unsigned int)(loops_per_us * 1000000 / targetf);
26 uint32_t tick_counter;
27 uint32_t dc[num_channels+1];
28 uint32_t tick2flip[num_channels+1];
29 uint32_t loop_counter;
30
31 String letterin;
32 char commandin[4]; // for command input
33 byte bytein[4];
34 byte channel2set;
35 uint32_t valin; // input 4 bytes = 1x int32
36
37
38 int i;
39
40 int j;
41 void setup() {
42   for (i = 1; i <= num_channels; i++) {
43     dc[i] = default_dc;
44     tick2flip[i] = ((float)(default_dc) / 100 * num_ticks);
45     pinMode(output_ch[i], OUTPUT);
46     digitalWrite(output_ch[i], LOW);
47   }
48
49   pinMode(redLED, OUTPUT);
50   pinMode(boardLED, OUTPUT);
```

slave_a_control_prog.ino

```
51
52   Wire.begin(myid);           // join i2c bus with address
53   Wire.onReceive(receiveEvent); // register event
54   if (serialdebugmode) {
55       Serial.begin(9600);      // start serial for output
56
57       for (j = 1; j <= num_channels; j++) {
58           Serial.print("#ticks of channel ");
59           Serial.print(j);
60           Serial.print(" :");
61           Serial.println(tick2flip[j]);
62       }
63   }
64 }
65
66 // all channel low when setup
67 for (j = 1; j <= num_channels; j++) {
68     digitalWriteFast(output_ch[j], LOW);
69 }
70
71 void loop() {
72     // set all to low
73
74     // for (j = 1; j <= num_channels; j++) {
75     //     if (tick2flip[j]) {
76     //         digitalWriteFast(output_ch[j], HIGH);
77     //     }
78     // }
79
80     // emitting PWM amplitude control signal
81     for (tick_counter = 0; tick_counter < num_ticks; tick_counter++) {
82         for (j = 1; j <= num_channels; j++) {
83             if (tick_counter > tick2flip[j]) {
84                 digitalWriteFast(output_ch[j], LOW);
85             }
86             else {
87                 digitalWriteFast(output_ch[j], HIGH);
88             }
89         }
90     }
91 }
92
93 }
94
95
96 void receiveEvent(int howMany)
97 {
98     digitalWrite(boardLED, HIGH); // start communication
99     digitalWrite(redLED, LOW);
100     letterin = "";
101 }
```

```

slave_a_control_prog.ino
102 // read command input
103 while (Wire.available() > 5) { // loop through all but the last 4 bytes
104 | letterin += (char)Wire.read(); // receive byte as a character
105 }
106 letterin.toCharArray(commandin, 4);
107
108 // read what channel to set
109 channel2set = Wire.read();
110 // read bytes input
111 bytein[0] = Wire.read(); // receive bytes
112 bytein[1] = Wire.read();
113 bytein[2] = Wire.read();
114 bytein[3] = Wire.read();
115
116 // convert to uint32_t
117 valin = 0;
118 valin = (uint32_t) bytein[0] << 24;
119 valin |= (uint32_t) bytein[1] << 16;
120 valin |= (uint32_t) bytein[2] << 8;
121 valin |= (uint32_t) bytein[3];
122
123 if (serialdebugmode) {
124 | Serial.println(commandin);
125 | Serial.print("channel to set: ");
126 | Serial.println(channel2set);
127 | Serial.print("bytes read:\n");
128 | Serial.println(bytein[0]); // print as integer
129 | Serial.println(bytein[1]); // print as integer
130 | Serial.println(bytein[2]); // print as integer
131 | Serial.println(bytein[3]); // print as integer
132 | Serial.print(">> ");
133 | Serial.print(valin);
134 | Serial.print("\n\n");
135 }
136 digitalWrite(boardLED, LOW); // end communication
137
138
139 // input translation
140 // strcmp returns 0 if the strings match
141
142 if (!strcmp(commandin, "dcy")) {
143 | dc[(int)channel2set] = valin;
144 | tick2flip[(int)channel2set] = ((float)valin / 100 * num_ticks);
145 | if (serialdebugmode) {
146 | | Serial.print("dcy set:: channel :");
147 | | Serial.print(channel2set);
148 | | Serial.print("DC:");
149 | | Serial.println(valin);
150 | }
151 | ledflash(redLED, 1);
152 }

```

```

slave_a_control_prog.ino
152     else if (!strcmp(commandin, "taf")) {
153         targetf = valin;
154         num_ticks = (unsigned int)(loops_per_us * 1000000 / targetf);
155         // update tick2flip values
156         for (j = 1; j <= num_channels; j++) {
157             tick2flip[j] = ((float)dc[j] / 100 * num_ticks);
158         }
159         ledflash(redLED, 2);
160     }
161
162
163     if (serialdebugmode) {
164         Serial.print("duty cycle set, Hz:");
165         Serial.print(targetf);
166         Serial.print(" #ticks:");
167         Serial.println(num_ticks);
168         for (j = 1; j <= num_channels; j++) {
169             Serial.print("#ticks of channel ");
170             Serial.print(j);
171             Serial.print(" :");
172             Serial.println(tick2flip[j]);
173         }
174         for (j = 1; j <= num_channels; j++) {
175             Serial.print("DC% of channel ");
176             Serial.print(j);
177             Serial.print(" :");
178             Serial.println(dc[j]);
179         }
180     }
181 }
182
183
184 else { // command not recognised
185     digitalWrite(boardLED, HIGH); // communication error or command not recognised
186 }
187
188 }
189
190
191 void ledflash(int pin, int blinks) {
192     for (int k = 0; k < blinks; k++) {
193         digitalWrite(pin, HIGH);
194         delay(half_led_blink_period_ms);
195         digitalWrite(pin, LOW);
196         delay(half_led_blink_period_ms);
197     }
198 }
199

```

Frequency Control_Slave_Boards:

slave_f_control_prog.ino

```
1 // ----- //
2 #define myid 1
3 #define serialdebugmode 0
4 #define half_led_blink_period_ms 150
5 #define internaldefaultdelay 40
6 // ----- //
7
8
9 //R Gemmell Teensy 4 I2C lib:
10 #include <i2c_device.h>
11 #include <i2c_driver.h>
12 #include <i2c_driver_wire.h>
13 #include <i2c_register_slave.h>
14
15 // #include <Wire.h>
16 #define boardLED 13
17 #define redLED 23
18 #define trigin 20
19 #define outputpin 4
20 // #define SCLpin 19
21 // #define SDApin 18
22
23
24 String letterin;
25 char commandin[4]; // for command input
26 byte bytein[4];
27 uint32_t valin; // input 4 bytes = 1x int32
28
29 // emission variables and default values
30 uint32_t freqHz = 500000;
31 uint32_t freqcount = 296; // 296 nops per 1us -- half period
32 uint32_t freqcounter = 0; // loop counter
33 uint32_t cyclecount = 0;
34 uint32_t cycles = 20;
35 uint32_t delayticks = (unsigned int)((float)(internaldefaultdelay) * 0.296);
36 uint32_t delaytick_counter = 0;
37
38 boolean IO = true;
39 void setup() {
40     pinMode(redLED, OUTPUT);
41     digitalWrite(redLED, HIGH);
```

```

42     pinMode(boardLED, OUTPUT);
43     digitalWrite(boardLED, LOW);
44
45
46     Wire.begin(myid);           // join i2c bus with address
47     Wire.onReceive(receiveEvent); // register event
48     if (serialdebugmode) {
49         Serial.begin(9600);      // start serial for output
50     }
51
52     pinMode(trigin, INPUT);
53     attachInterrupt(digitalPinToInterrupt(trigin), PUL, RISING);
54
55     pinMode(outputpin, OUTPUT);
56     digitalWrite(outputpin, LOW);
57 }
58
59 void loop() {
60     //Interrupt();
61     //delay(100); // ms
62     //Serial.println("waiting ...");
63 }
64
65
66 void receiveEvent(int howMany)
67 {
68     digitalWrite(boardLED, HIGH); // start communication
69     digitalWrite(redLED, LOW);
70     letterin = "";
71
72     // read command input
73     while (Wire.available() > 4) { // loop through all but the last 4 bytes
74         letterin += (char)Wire.read(); // receive byte as a character
75     }
76     letterin.toCharArray(commandin, 4);
77
78     // read bytes input
79     bytein[0] = Wire.read(); // receive bytes
80     bytein[1] = Wire.read();
81     bytein[2] = Wire.read();
82     bytein[3] = Wire.read();
83
84     // convert to uint32_t
85     valin = 0;
86     valin = (uint32_t) bytein[0] << 24;
87     valin |= (uint32_t) bytein[1] << 16;
88     valin |= (uint32_t) bytein[2] << 8;
89     valin |= (uint32_t) bytein[3];
90
91     if (serialdebugmode) {
92         Serial.print(commandin);
93         Serial.print("bytes read:\n");
94         Serial.println(bytein[0]); // print as integer
95         Serial.println(bytein[1]); // print as integer
96         Serial.println(bytein[2]); // print as integer
97         Serial.println(bytein[3]); // print as integer
98         Serial.print(">> ");
99         Serial.print(valin);
100        Serial.print("\n\n");

```

```

101     }
102     digitalWrite(boardLED, LOW); // end communication
103
104
105     // input translation
106     // strcmp returns 0 if the strings match
107 > if (!strcmp(commandin, "frq")) { ...
108     }
109     else if (!strcmp(commandin, "cyc")) {
110         cycles = valin;
111         if (serialdebugmode) {
112             Serial.print("cyc set:: cycles:");
113             Serial.println(cycles);
114         }
115         ledflash(boardLED, 2);
116     }
117     else if (!strcmp(commandin, "dly")) {
118         delayticks = (unsigned int)((float)(valin + internaldefaultdelay) * 0.296);
119         if (serialdebugmode) {
120             Serial.print("dly set:: ns delay:");
121             Serial.print(valin);
122             Serial.print("#ticks:");
123             Serial.println(delayticks);
124         }
125         ledflash(boardLED, 3);
126     }
127     else if (!strcmp(commandin, "onf")) {
128         if (valin) {
129             IO = true; // enable this channel
130             if (serialdebugmode) {
131                 Serial.println("onf set:: channel ON");
132             }
133         }
134         else {
135             IO = false; // disable this channel
136         }
137         if (serialdebugmode) {
138             Serial.println("onf set:: channel OFF");
139         }
140     }
141     else { // command not recognised
142         digitalWrite(boardLED, HIGH); // communication error or command not recognised
143     }
144
145     // display whether this channel is enabled
146     // when the red LED is ON, the channel is disbled
147     if (IO) {
148         digitalWrite(redLED, HIGH);
149     }
150     else {
151         digitalWrite(redLED, LOW);
152     }
153
154     prepareforinterrupt();
155 }
156
157
158

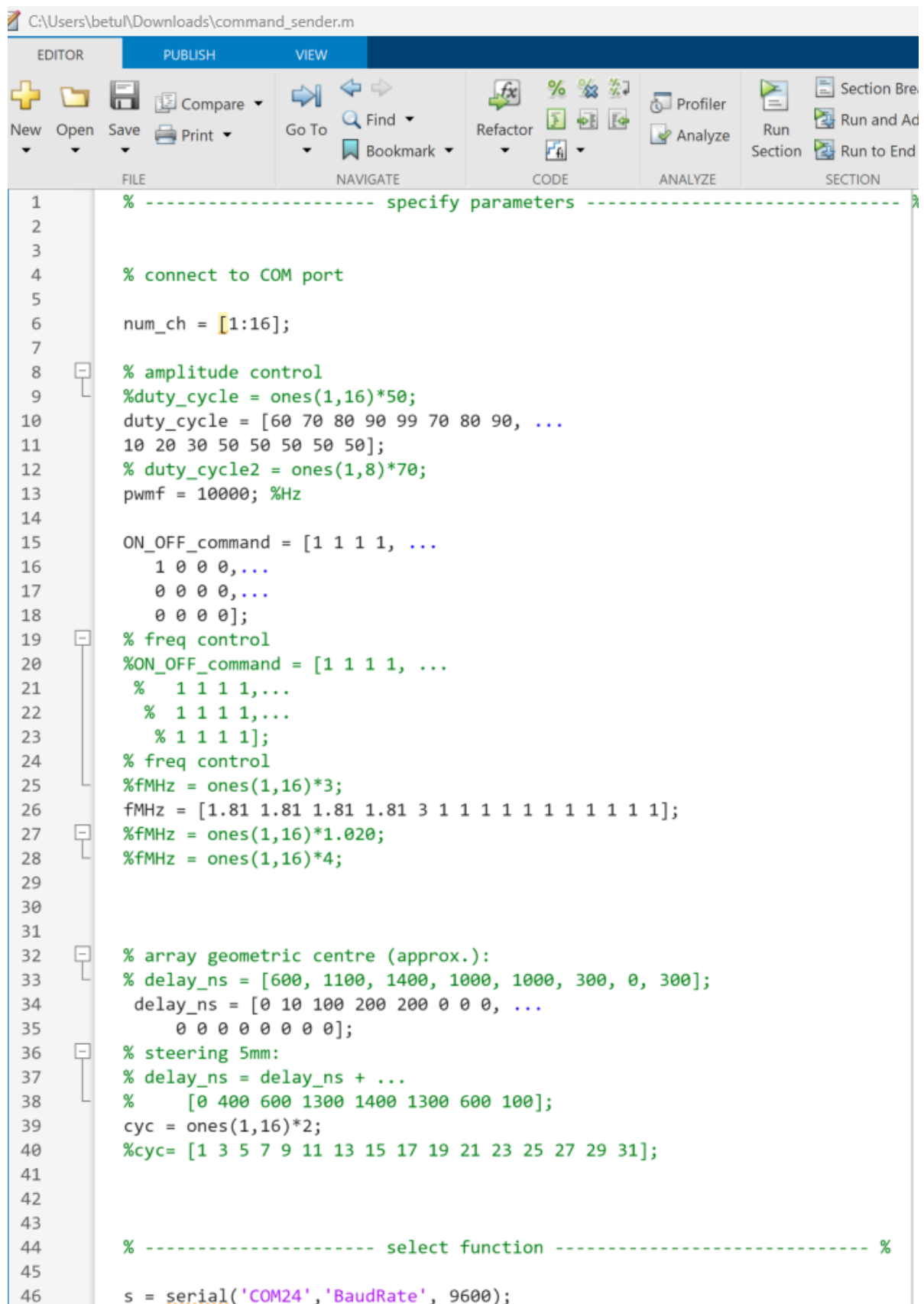
```

```

168 void ledflash(int pin, int blinks) {
169     for (int k = 0; k < blinks; k++) {
170         digitalWrite(pin, HIGH);
171         delay(half_led_blink_period_ms);
172         digitalWrite(pin, LOW);
173         delay(half_led_blink_period_ms);
174     }
175 }
176
177
178 void PUL() {
179     //
180     if (IO) {
181         // target_nop = (target_period_us-0.0216)/0.0033
182         // corrected equation = 1/296 us per nop
183
184         // initial delay for steering
185         for (delaytick_counter = 0; delaytick_counter < delayticks; delaytick_counter++) {
186             __asm__ __volatile__ ("nop\n\t");
187         }
188
189         // emitting frequency signal
190         for (cyclecount = 0; cyclecount < cycles; cyclecount++) {
191
192
193             digitalWriteFast(outputpin, HIGH);
194             for (freqcounter = 0; freqcounter < freqcount; freqcounter++) {
195                 __asm__ __volatile__ ("nop\n\t");
196             }
197             digitalWriteFast(outputpin, LOW);
198             for (freqcounter = 0; freqcounter < freqcount; freqcounter++) {
199                 __asm__ __volatile__ ("nop\n\t");
200             }
201
202         }
203
204         digitalWrite(redLED, LOW);
205         delay(150);
206         digitalWrite(redLED, HIGH);
207     }
208     else { // IO OFF
209         digitalWriteFast(outputpin, LOW);
210     }
211 }
212
213
214 void prepareforinterrupt()
215 {
216     if (IO) {
217         for (delaytick_counter = 0; delaytick_counter < delayticks; delaytick_counter++) {
218             __asm__ __volatile__ ("nop\n\t");
219         }
220         for (cyclecount = 0; cyclecount < cycles; cyclecount++) {
221             for (freqcounter = 0; freqcounter < freqcount; freqcounter++) {
222                 __asm__ __volatile__ ("nop\n\t");
223             }
224         }
225     }
226 }
227

```

MATLAB codes to control parameters:



```

C:\Users\betul\Downloads\command_sender.m
EDITOR PUBLISH VIEW
New Open Save Compare Print Go To Find Refactor Profiler Run Run and Ad
FILE NAVIGATE CODE ANALYZE SECTION
1 % ----- specify parameters -----
2
3
4 % connect to COM port
5
6 num_ch = [1:16];
7
8 % amplitude control
9 %duty_cycle = ones(1,16)*50;
10 duty_cycle = [60 70 80 90 99 70 80 90, ...
11 10 20 30 50 50 50 50];
12 % duty_cycle2 = ones(1,8)*70;
13 pwmf = 10000; %Hz
14
15 ON_OFF_command = [1 1 1 1, ...
16 1 0 0 0,...
17 0 0 0 0,...
18 0 0 0 0];
19 % freq control
20 %ON_OFF_command = [1 1 1 1, ...
21 % 1 1 1 1,...
22 % 1 1 1 1,...
23 % 1 1 1 1];
24 % freq control
25 %fMHz = ones(1,16)*3;
26 fMHz = [1.81 1.81 1.81 1.81 3 1 1 1 1 1 1 1 1 1 1];
27 %fMHz = ones(1,16)*1.020;
28 %fMHz = ones(1,16)*4;
29
30
31
32 % array geometric centre (approx.):
33 % delay_ns = [600, 1100, 1400, 1000, 1000, 300, 0, 300];
34 delay_ns = [0 10 100 200 200 0 0 0, ...
35 0 0 0 0 0 0 0];
36 % steering 5mm:
37 % delay_ns = delay_ns + ...
38 % [0 400 600 1300 1400 1300 600 100];
39 cyc = ones(1,16)*2;
40 %cyc= [1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31];
41
42
43
44 % ----- select function ----- %
45
46 s = serial('COM24','BaudRate', 9600);

```

```

47     fopen(s);
48
49
50
51     %setmaster(s,'dcy',duty_cycle,num_ch, 0.25)
52     setmaster(s,'freq',calibrate_f_input(fMHz),num_ch,0.25)
53     %setmaster(s,'cyc',cyc,num_ch, 0.25)
54     %setmaster(s,'freq',fMHz,num_ch,0.25)
55     %setmaster(s,'io',ON_OFF_command,num_ch,0.25)
56     setmaster(s,'dly',delay_ns,num_ch,0.25)
57     fclose(s);
58
59     return
60
61     %% trg
62     fopen(s);
63     fprintf(s,'% ');
64     fclose(s);
65
66     %%
67     (calibrate_f_input([0.25 0.5 0.75 1]))/1e3
68
69
70     %%
71     function setmaster(s,cmdout,val,num_ch,delay_s)
72     for ch = num_ch
73         commandout = [cmdout,':',num2str(ch),':',num2str(val(ch))];
74         fprintf(s,commandout);
75         str2double(fscanf(s))
76         pause(delay_s);
77     end
78 end
79
80
81
82     function Hz_command = calibrate_f_input(MHz_target)
83
84     % in out
85     % 100 101.1
86     % 250 251.8
87     % 500 500
88     % 750 747
89     % 1020 1000
90     % 3000 2845
91     % 3100 2899
92     in = [100 250 500 750 1020 3000 3100];
93     out = [101.1 251.8 500 747 1000 2845 2899];
94     %plot(in,out);
95     Hz_command = interp1(in,out,MHz_target*1e3)*1e3;
96
97
98     end

```