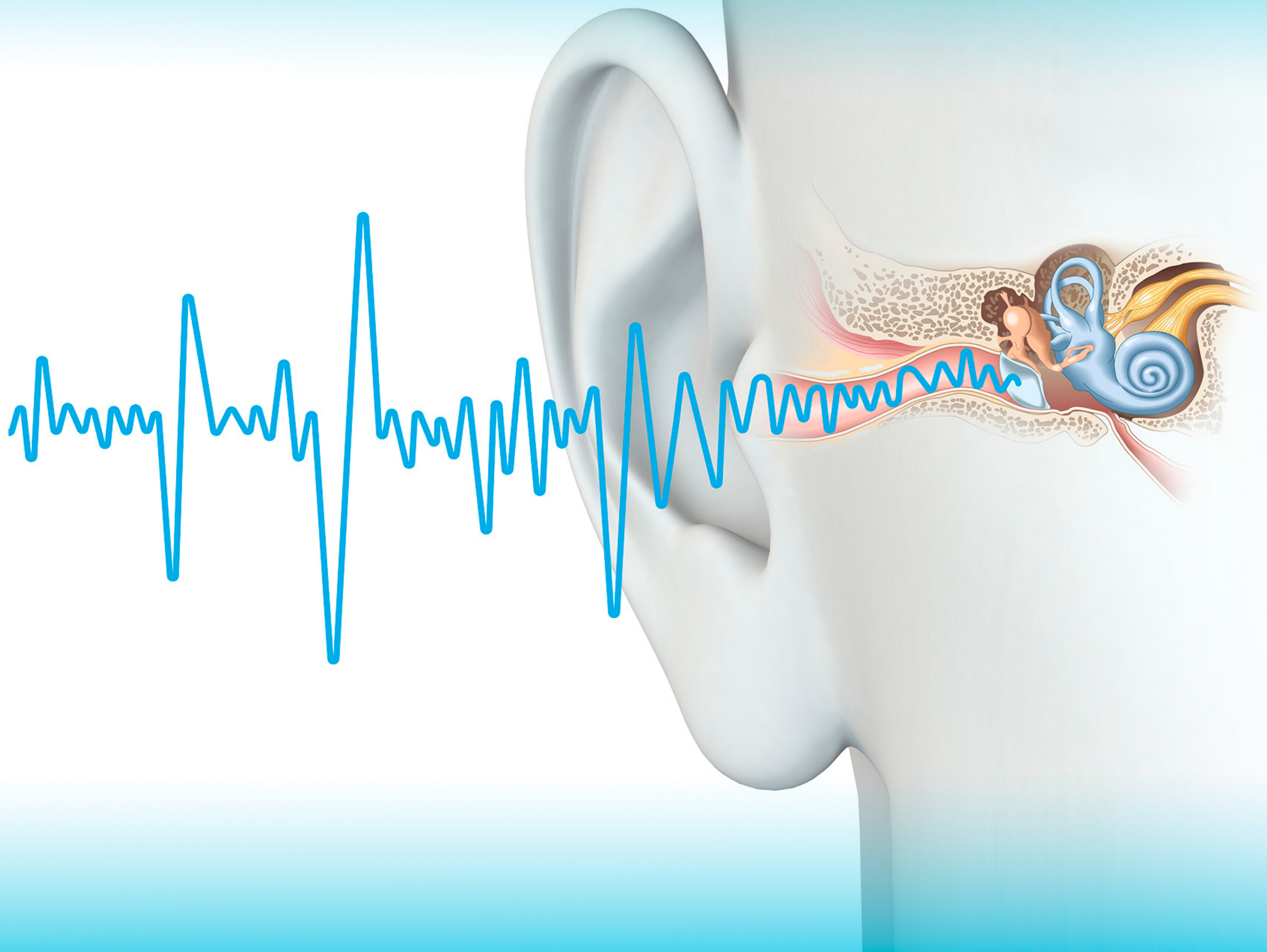
Design of a novel multi-modal stimulation device for the treatment of tinnitus

A.Barbon Pedrina



Technische Universiteit Delft

Design of a novel multi-modal stimulation device for the treatment of tinnitus

by

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Abstract

Approximately 15-20% of the world population is affected by tinnitus, a hearing condition associated with phantom sound perception. A large number of sufferers experience a severe level of tinnitus and they are not able to conduct a normal life because they develop insomnia, depression, and distress.
Extensive research has been made to study its pathophysiology and to find a therapy. However, currently there are no treatments that have demonstrated to be effective in modulating tinnitus or suppressing its related annoyance from a long-term perspective. What is known is that the patients exhibit abnormal electrical activity in multiple areas of the auditory and the central nervous systems. This is the reason why the focus of the scientists has shifted to multi-modal stimulation: multiple stimulations of equal or different nature (e.g. double electrical stimulation or acoustic-electrical stimulation) are applied at the same time in the attempt to induce neuroplasticity and restore the normal electrical activity in the targeted areas. Multi-modal stimulation has brought significant improvements both in terms of tinnitus intensity and distress, but the studies conducted are too little to derive conclusions. Stimulation sites, parameters, and patterns are some of the many issues that have to be properly investigated.
The challenge of this work is to design a portable multi-modal stimulator that is able to provide bilateral acoustic and electrical stimulation simultaneously. The device works at the same time as an audio player and a transcutaneous electrical nerve stimulator, with the purpose of contemporaneously stimulating the auditory cortex and the autonomic nervous system or the dorsal cochlear nucleus through the vagal nerve or the C2 nerve, respectively.
Bi-modal stimulation is based on the random presentation of pure tones matched to the tinnitus frequency pitch combined with two possible electrical stimulation waveforms: a novel one characterized by the superposition of a low-frequency noise on a DC component ("noise + DC" stimulation) and the second one is burst stimulation. Both the electrical stimulations are current-driven and largely customizable due to the wide programmability of the stimulation parameters. The analog design is realized in such a way that two identical output currents are delivered to the tissue, allowing for bilateral stimulation.
The low power consumption and the small dimensions and weight of the device will permit the tinnitus patient to use it for several hours per day while performing his daily life without impairments.

Acknowledgement

TU Delft university is an important step in my life: it is indeed the first long study experience that I made abroad and also the experience that made me grow the most both in terms of technical knowledge and as a person. Even if the second academic year was brutally changed by the COVID pandemic, the people that I met and that were surrounding me have been fundamental for finishing this experience in a great manner, especially as regards the thesis project.

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Contents

List of Tables ix

List of Figures xi

1 Introduction 1

2 Literature study 3

2.1 Anatomy and physiology of the auditory system . . . 3

2.2 Possible pathophysiological explanations behind tinnitus . . . 7

2.2.1 Pathophysiology in the peripheral auditory system . . . 8

2.2.2 Pathophysiology in the central auditory system and predictive coding model . . . 9

2.2.3 Roles played by non-auditory brain regions . . . 10

2.3 Currently available treatments for tinnitus . . . 12

2.3.1 Approaches based on electrical stimulation. . . . 16

2.3.2 Treatments involving multi-modal stimulation . . . 21

3 Device specifications 25

3.1 General idea . . . 25

3.2 Device functions . . . 26

3.3 Stimulation sites . . . 26

3.4 Stimulation therapies. . . . 28

3.4.1 Parameters for multi-modal burst stimulation (T1) . . . 28

3.4.2 Parameters for multi-modal "noise + DC" stimulation (T2) . . . 30

3.4.3 Combined mode (T3) . . . 31

3.5 Stimulation duration . . . 31

3.6 Power source. . . . 31

3.7 Compliance voltage . . . 32

3.8 Other requirements . . . 32

4 General architecture and system block diagram 35

5 Device design: hardware 39

5.1 External memory storage and communication protocol . . . 39

5.2 Electrical stimulation circuit 41
5.2.1 Digital-to-analog converter. 41
5.2.2 Pulse Width Modulation and PWM DAC 44
5.2.3 Circuit for "Noise + DC" stimulation 49
5.2.4 Voltage-to-current converter and current driver 52
5.2.5 Circuit for bidirectional stimulation 57
5.3 Microcontroller 58
5.3.1 Architecture of the ATMEGA 328P Timers 61
5.4 Circuit for acoustic stimulation. 63
5.5 Power management 65

6 Device design: software 69
6.1 Digital sound processing 69
6.2 Programming the microcontroller: algorithm for synchronous multi-modal stimulation and sound generation. 70

7 Validation tests 73
7.1 Measurement setup 73
7.2 Stimulation waveforms and frequency spectrum of "noise + DC" waveform 74
7.3 Accuracy of the DC output current. 76
7.4 Synchronization of current and sound generator outputs. 78
7.5 Power consumption 81
7.6 Validation tests of the sound generator. 82

8 Conclusions and recommendations 85

A Design and fabrication of the PCBs 89

B Experimental setup 93

C Arduino programs 95

D Boost converter module 101

Bibliography 103

List of Tables

3.1 Summary of the device specifications 34

5.1 Comparison of the different implementations of a digital-to-analog conversion block 49
5.2 Technical specifications of Arduino Uno board [125] 59

8.1 Final specifications of the multi-modal stimulator 87

List of Figures

2.1 Peripheral auditory system [11] 3
2.4 The two possible laser therapies experimented for tinnitus 14
2.5 Examples of noise colours used in sound therapy [2] 15
2.6 Examples of treatments based on electrical stimulation for tinnitus 24

3.1 Multi-modal stimulation: stimulation sites 27
3.2 Multi-modal stimulation: proposed design for the "auxiliary" component for tragus stimulation 27
3.3 Burst stimulation present in T1 29
3.4 Noisy pseudo DC waveform present in T2 30
3.5 Combined therapy present in T3 (each pulse is equal to one burst) 31

4.1 Block diagram of the multi-modal stimulator 36

5.1 SPI communication between an SD card and a microcontroller 40
5.2 Architecture of a String DAC [68] 42
5.3 Principles of a digital potentiometer 43
5.4 Representation of a Pulse Width Modulated signal 45
5.5 First-order passive low pass filter [55] 45
5.6 First-order passive low pass filter followed by a buffer amplifier 48
5.7 Circuit used to realize the "noise+ DC" waveform 50
5.8 Details of the "noise + DC" stimulation circuit 52
5.9 The improved Howland current pump 53
5.10 The transconductance amplifier combined with an "improved" double-output current mirror based on PNP bipolar transistors 54
5.11 Input-output relation of the transconductance amplifier combined with the "improved" double-output current mirror (loads over the two outputs R_{load1} = R_{load2} = 1 $k\Omega$) 56
5.12 Final output stage in the current generator of the multi-moda stimulator based on 2 H-Bridge configurations 57
5.13 Architecture of the ATMega328 Timer 0 present in the Arduino Uno [22] 61
5.14 Blocks composing the Timer 0 of ATMega328: Counter Unit (top left), Output Compare Unit (top right), and Compare Match Output Unit (bottom) [22] 63
5.15 Circuital design of the sound generator 64

5.16 Architecture of a boost converter: boost converter working in phase 1 (left) and boost converter working in phase 2 (right) [75] . . . 66

6.1 Stereo track generated in Audacity: the signal on top is the sequence of tones, while the one at the bottom is the noisy signal . . . 70

7.1 Stimulation waveforms of the multi-modal stimulator visible in the PC Oscilloscope . . . 75
7.2 Frequency spectrum of the "noise + DC" output signal . . . 76
7.3 Output currents as a function of programmed input in the current generator (load R_{load} = 1 kΩ, F_{PWM} = 160 kHz) . . . 77
7.4 Measured errors of the output currents with respect to the programmed input . . . 77
7.5 Dependency of the output currents on the load . . . 78
7.6 Simultaneous acoustic and burst stimulation waveforms (F_{TONE} = 50 Hz, F_{spike} = 50 Hz, F_{burst} = 5 Hz, programmed current I = 2 mA, intermittent stimulation t_{ON} = 1 s and t_{OFF} = 1 s) . . . 79
7.7 Simultaneous acoustic and "noise + DC" stimulation waveforms (last two figures, F_{TONE} = 50 Hz, programmed current I = 2 mA, intermittent stimulation t_{ON} = 1 s and t_{OFF} = 1 s) . . . 80
7.8 Power consumption of the current generator: (including consumption of the Arduino and the micro SD card): burst stimulation (left, F_{spike} = 50 Hz, F_{burst} = 5 Hz), "noise + DC" stimulation (right, phase duration t_{DC} = 10 s) . . . 81
7.9 Pie Chart describing the power consumption of the multi-modal stimulator (worst case scenario: Burst stimulation with programmed current 2 mA and max audio volume) . . . 82
7.10 Portions of the output PWM waveform of the sound generator: output waveform with PWM frequency 16 kHz (left), Output waveform with PWM frequency 32 kHz (right) . . . 83
7.11 Frequency spectrum of the PWM output audio signal encoding a 2000 Hz sinusoidal tone . . . 84

A.1 PCB layout of the circuit for acoustic stimulation . . . 89
A.2 PCB layout of the circuit for electrical stimulation . . . 90
A.3 Immersion of the PCB in sodium hydroxide after UV exposure . . . 90
A.4 PCB drilling . . . 91
A.5 PCB sawing . . . 91
A.6 Final PCB for acoustic stimulation . . . 92
A.7 Final PCB for electrical stimulation . . . 92

B.1 Experimental setup used to test the circuit for electrical stimulation . . . 93

C.1 Arduino code for intermittent acoustic and burst stimulation (1) . . . 95
C.2 Arduino code for intermittent acoustic and burst stimulation (2) . . . 96
C.3 Arduino code for intermittent acoustic and burst stimulation (3) . . . 97
C.4 Arduino code for intermittent acoustic and burst stimulation (4) . . . 98

C.5 Arduino code for intermittent acoustic stimulation and non-intermittent "noise + DC" stimulation (1) . . . 99
C.6 Arduino code for intermittent acoustic stimulation and non-intermittent "noise + DC" stimulation (2) . . . 99
C.7 Arduino code for intermittent acoustic stimulation and non-intermittent "noise + DC" stimulation (3) . . . 100
C.8 Arduino code for intermittent acoustic stimulation and non-intermittent "noise + DC" stimulation (4) . . . 100

D.1 Circuit of the MT3608 boost converter module . . . 101

1 Introduction

Tinnitus represents a condition in which a phantom sound is perceived in the ears without being linked to any environmental source. According to estimations, approximately 15-20% of the global population suffers from tinnitus, and a significant part of it is affected by the disorder in such a way that it cannot lead a daily life. Indeed, depression, anxiety, insomnia, and suicidal attempts often follow severe tinnitus [17].

Although a clear origin has not been defined yet, it has been demonstrated that locations of the auditory system and others in the central nervous system exhibit abnormal electrical activity in the people suffering from tinnitus, making clear their involvement in the manifestation of this disorder. However, despite numerous studies and experiments an effective and long-lasting treatment has not been discovered yet. Drug treatment, surgery, counseling, laser therapy, sound therapy, and electrical stimulation have shown mixed results and none of them have brought to complete tinnitus suppression.

The attention of the scientists is currently addressed to a treatment that is being investigated in the last years: multi-modal stimulation. Multi-modal stimulation aims to contemporaneously stimulate (either electrically or with stimuli of different nature) multiple areas of the body in the attempt to restore the normal electrical activity of the brain. Promising outcomes have been obtained by the application of multi-modal stimulation, both in terms of tinnitus intensity and annoyance reduction. Nevertheless, it is too early to derive conclusions since the number of experiments conducted is too little and there are not many devices that are being developed for this purpose.

The work explained in the report refers to the design of a device for multi-modal stimulation that is the consequence of the following research question:

Is it possible to design a portable device that is able to provide bilateral acoustic and electrical stimulation simultaneously?

According to the need of Dr. De Ridder, who collaborates in this project, the multi-modal stimulator will work at the same time as an audio player and as a TENS device, with the purpose of contemporaneously stimulating the auditory cortex and the vagal nerve or the C2 nerve (depending on the position of the electrodes). The device has to deliver a therapy based on the random presentation of pure tones combined with electrical stimulation. The electrical stimulation is based on a novel waveform composed of the combination of a low-frequency noise and a DC component ("noise + DC" stimulation). Moreover, the device allows to perform electrical burst stimulation and will be therefore used to compare the effectiveness of the two stimulation patterns.

The report is organized as follows:

- **Chapter 2** contains the literature study that has been conducted prior to the design of the device. Three sections are present to describe the auditory system from an anatomical and physiological point of view, the possible physiological mechanisms and areas that exhibit abnormal activity in tinnitus patients. Finally, a denser portion is dedicated to the treatments that have been experimented with and are still under investigation aiming to modulate or suppress tinnitus. Particular attention is given to electrical stimulation and multi-modal stimulation;
- **Chapter 3** specifies the requirements of the device;
- **Chapter 4** presents an overview of the system design and an explanation of the building blocks that constitute the multi-modal stimulator;
- **Chapter 5** analyzes each block of the system design and the choices and solutions for the analog design of the device;
- **Chapter 6** is dedicated to the software part of the design and in particular the creation of the audio file used for stimulation and the programming of the microcontroller;
- The validation tests and the assessment of the functionality of the device are described in **Chapter 7**;
- Finally, **Chapter 8** discusses to what extent the desired device specifications have been met and proposes future work and improvements.

2

Literature study

2.1. Anatomy and physiology of the auditory system

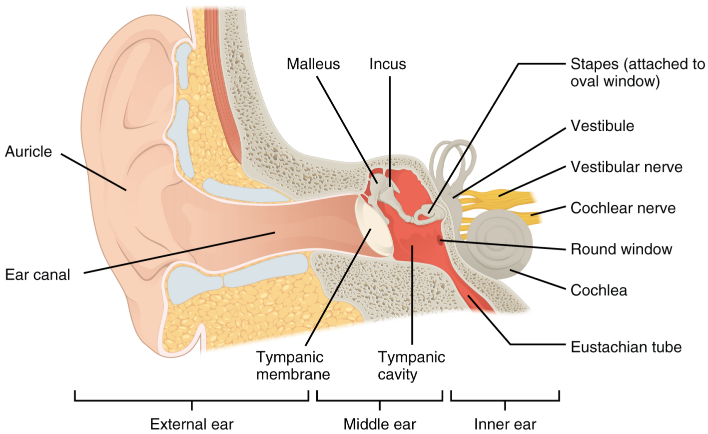


Figure 2.1: Peripheral auditory system [11]

The auditory system includes several organs of the body which are responsible for the reception, transmission, and perception of a sound.
The peripheral auditory system involves those body structures that are capable of capturing a certain sound coming from the external environment and transmit the information about the sound to the brain structures in order to be processes and perceived. Those structures are the outer, middle, inner ear, and the cochlear nerve.
The pinna and the auditory canal form the *outer ear* . The pinna is the part of the ear visible from the outside and made of fibrocartilage which thanks to its oval shape allows the soundwaves to enter the auditory system and to be filtered depending on their incidence angle. Once entered the pinna, the soundwave propagates through the

auditory canal and reaches the tympanic membrane. The tympanic membrane is a cone-shaped membrane that vibrates whenever a soundwave hits it. Its vibrations are essential because they permit the sound to propagate towards the middle ear and the inner ear; indeed, the movements of the tympanic membrane spread towards the three ossicles of the *middle ear*, named malleus, incus, and stapes. The stapes is connected to the inner ear via a kidney-shaped opening covered by a membrane, called oval window. The middle ear includes also the Eustachian tube, which is a bony and cartilaginous structure that connects the auditory system to the nasopharynx and has a relevant function for the peripheral auditory system: when a person swallows or yawns, the muscles open the normally closed tube allowing for a pressure exchange between the middle ear and the other side of the tube; in this way, the same level of atmospheric pressure is ensured both inside and outside the tympanic membrane, maintaining an equilibrium important for the free movements of the membrane and the three ossicles.

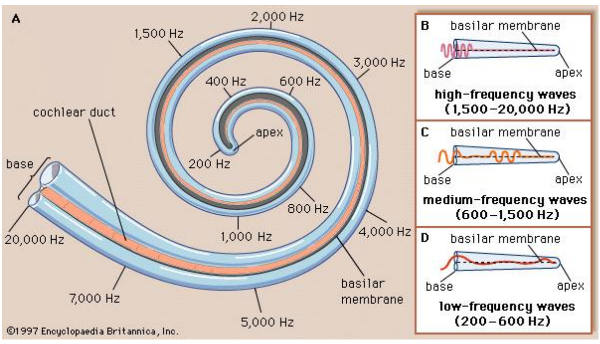
The *inner ear* is entirely described by the cochlea, the real "sensor" of the human auditory system, which is able to convert the vibrations generated by a sound into an electrical signal. It is a spiral-shaped cavity filled with different fluids which contains the organ of hearing, i.e. the organ of Corti. The organ of Corti crosses all over the length of the cochlea and is populated by sensory receptors called hair cells, which realize the electromechanical transduction of the sounds. The hair cells are located in the space between the tectorial and basilar membrane, the two membranes that determine the structure of the organ of Corti.

When the stapes moves due to the vibrations of a soundwave, it causes the flow forward and back into the cochlea of a fluid called endolymph. In turns, the endolymph generates the movements right and left of the basilar membrane and consequently of the hair cells. In particular, the hair cells contain stereocilia (hair bundles) that whenever they move cause the K^+ and Ca^{2+} ion channels to open. As a consequence, the ions start flowing into the cells increasing their membrane potential until the point at which an action potential is generated.

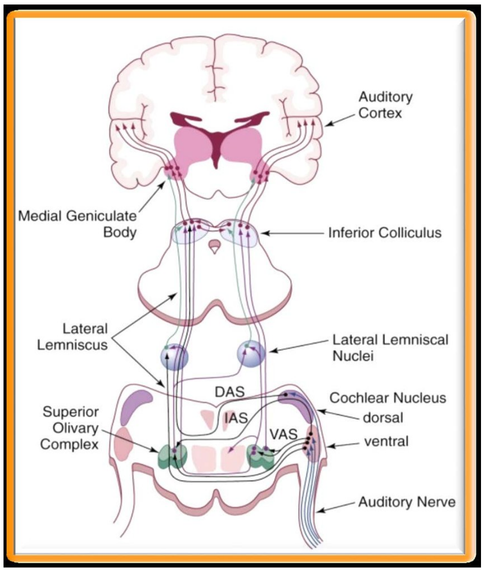
Actually, not all the hair cells are mechanotransducers, but only a subgroup called inner hair cells. The other subgroup is formed by cells called outer hair cells that play another important role in the sound transmission; indeed, the outer hair cells do not generate an action potential, but their mechanical stimulation determines a variation in the shape of their cell bodies which mechanically amplify the acoustical inputs. Therefore, they are especially important when the sound intensity is low and the vibrations would not be sufficient to stimulate the inner hair cells. Indeed, the pressure changes over time which are generated by the sound transmission are especially present when the sound reaches the inner ear [34]; in that region the conductive medium changes from air to the endolymph (which is denser, and so less conductive in terms of pressure transfer) and, as a consequence, the increased acoustic impedance causes a drop in the sound intensity of around 35 dB, which therefore in some cases requires an amplification.

Unlike the inner hair cells which are all connected to a large number of afferent fibers, the outer hair cells are primarily linked to efferent fibers; when an external potential is transmitted via the efferent fibers, they contract modifying their amplification properties. This is used as a active feedback loop to vary the sensitivity and frequency selectivity of the cochlea [3][69].

The flow of the endolymph inside the cochlea can stimulate hair cells in different locations depending on the frequencies of the acoustic signal: the lower components of the acoustic spectrum tend to stimulate the inner hair cells located in the apex, while the higher components do not overcome the base [34]. Basically each location of the basilar membrane is associated to one frequency, named the characteristic frequency. In this way, a sort of map of the frequencies forms in the cochlea, called tonotopic map (visible in Fig. 2.2a), which help maintain the components of a sound separated one to the other. The tonotopicity is preserved for the all pathway of the auditory system allowing the auditory cortex to elaborate each sound frequency distinctly [92]. The peripheral auditory system concludes with the *cochlear nerve*, which is formed by around 30000 nerve fibers which fire depending on the firing rate of the inner hair cells they are connected to [3][103]. Via its fibers the cochlear nerve spreads the action potentials towards the central auditory system synapsing within the cochlear nucleus [95]. Two type of neurons are present in the nerve: the great majority of them are myelinated and receive afferent inputs from the inner hair cells, while the others are unmyelinated and convey electrical stimuli to the outer hair cells [110].



(a) Tonotopic organization within the cochlea [20]



(b) Pathway of the central auditory system [4]

After the cochlear nerve, the acoustic information are transmitted to the nuclei in the brain regions and finally to the auditory cortex, a neural pathway called central auditory system. The central auditory system contains the following nuclei:

- *Cochlear nucleus*: first brain part of the central auditory pathway, it is the nucleus in which the cochlear nerve ends, bifurcating in two branches that synapse in the dorsal cochlear nucleus (DCN) and in the ventral cochlear nucleus (VCN) [37]. A tonotopic map is present also in this structure, where low-frequency signals reach the VCN while high frequencies the DCN creating a sort of gradient that goes from the ventral to the dorsal region of the nucleus [102]. Parallel to the map, there are special cells which deal with other characteristics of the sound and communicate through an ascending pathway with the inferior culliculus and the superior olivary complex, sending respectively monaural and binaural information [56].

Experiments have demonstrated that the DCN is connected to the somatosensory system; indeed, if the ear is mechanically stimulated (and consequently the trigeminal nerve), an inhibition of the electrical activity is verified in the DCN cells. Moreover, hyperactivity in the DCN has been shown in people suffering from some hearing problems such as tinnitus, suggesting an important involvement of this structure in these situations [8][129];

- *Superior olivary complex*: this cluster of nuclei found in the brainstem has a particularly significant role in the sound localization; indeed, the sound information coming from both ears converge in this structure, which is able to understand the location of the sound source based on the time difference and the intensities of the acoustic signals coming bidirectionally. The superior olivary complex has a property called coincidence detection: its anatomical organization permits the signals from the contralateral ear to reach its cells almost at the same time as the one from the ipsilateral ear allowing them to count as a single sound coming from a contralateral location in the environment [95][56];

- *Inferior culliculus*: located in the tectum of the midbrain and bordering ventrally the lateral lemnniscus, it is the largest nucleus of the auditory system [6]. In this nucleus several sound information including sound localization, frequency spectrum, intensity, and timing are integrated in order to have a full representation of an acoustic stimulus in the neural domain [83]. Furthermore, it is demonstrated to play a key role in the audio-visual integration of speech stimuli and in the detection of infrequent stimuli (ability called stimulus-specific adaptation) through the inhibition of the firing rate of its neurons caused by frequent stimuli and their activation when uncommon one are present [35][74][15];

- *Medial geniculate nucleus*: it is a little prominence in the acoustic thalamus and represents the thalamic point of communication between the inferior culliculus and the auditory cortex. The nucleus can be divided into three parts that distinguish for functions and region of communication. The anterior division is tonotopically organized (low frequency laterally, high frequency medially) and sends afferents to the primary auditory cortex. It is believed to be interested in the elaboration of complex sound features, since most of its neurons do not respond to simple tones. The communication with the secondary auditory cortex is reserved to the posterior division, whose cells are more easily fired and prone to habituation. It may be responsible for the auditory attention due to the recognition of unusual signals. Finally, the last portion of the medial geniculate nucleus is the medial one, which convey information to the association areas of the auditory cortex including the amygdala, the putamen, etc. The neurons present in this division fire both in response to auditory and stimuli of other nature. For this reason, it is hypothesized to be part of the reticular activating system and therefore to be involved in behaviour and sleep [56].

Eventually, the last component of the central auditory system is the *auditory cortex*, which occupies the upper portions of both the temporal lobes. The subdivision of the auditory cortex includes three functional regions. Between all the functions, the primary auditory cortex (A1) has to interpret the information encoded in the tonotopic map transported by the afferents coming from the medial geniculate body. Perpendicular to the tonotopic map in A1 there are neurons distributed in striped that exhibit binaural properties: one stripe

seems to be fired by stimuli from both ears, while the following one only by one ear and inhibited by the other. The secondary auditory cortex (A2) seems not to be tonotopically arranged but to participate in the elaboration of complex sound structures (such as the human language), in the spatial detection of the acoustic signals, and in the acoustic memory. Finally, A1 and A2 are encircled by the belt region, which does not have a tonotopical arrangement and is characterized by a great firing rate of its neurons in response to noisy stimuli. It is one of the regions responsible for the integration of acoustic and other sensory stimuli [44][124].
The functions executed by the other subdivisions of the auditory cortex are still under investigation, however some seem to be involved in the elaboration of natural sounds and other in elementary speech sounds and music. Some areas seem to be related to the elaboration of combinations of frequencies, and other to process modulations of intensity and frequency. Despite this, a lot of studies must still be conducted in order to discover step by step all the potentialities of the auditory cortex [99][10][87].

2.2. Possible pathophysiological explanations behind tinnitus

Tinnitus describes a condition in which a person perceives a sound ringing in the ear without being associated to any environmental source. It is therefore a phantom auditory perception, which is considered a symptom rather than a disease [53]. Numerous studies have been and are currently being conducted in the attempt to determine the mechanisms that bring to the manifestation of tinnitus. Unfortunately, right now there is not a well defined cause, but it seems that several sound-processing areas are involved simultaneously in its generation.
A first distinction that may help in characterizing it is the difference between pulsatile and non-pulsatile tinnitus. When the sound is perceivable by an external person via a stethoscope, it means that the tinnitus has a somatic origin, linked generally with the musculo-skeletal or vascular system; in this case, it is called *pulsatile tinnitus*. Pulsatile tinnitus is generally perceived as a rhythmical noise, often having the same frequency as the heart rate. Possible explanations are a venous hum, a high jugular bulb, an A-V malformation, an aneurysm, or a stenosis [57]. Nevertheless, scientists tend to associate automatically the concept of tinnitus with the *non-pulsatile* one, due to the fact that its origin is often not clear and unique, but it may involve more than one component of the auditory system. Non-pulsatile tinnitus occurs as a tonal or white noise sound which can only be heard by the sufferer himself [53] [17][50].
The first hypotheses concerning tinnitus generation were in favour of a cochlear origin, based on the fact that the sound can be perceived in the ears and that there is a correspondence between the tinnitus frequency spectrum and the frequency profile of people with hearing loss obtained via audiometry [106].
However, this could not be a reliable explanation due to the fact that if a surgery is perfomed in the auditory nerve or in the inner or middle ear (e.g. stapedecotomy, tympanosympathectomies, etc), the sound is not suppressed but on the contrary it may worsen [58]. Therefore, this consideration gave light to the involvement of sound processing mechanisms in the central nervous system [50].
Nowadays, more elaborated theories have been formulated that imply a more complex interaction between peripheral and central regions. In particular, tinnitus seems to be associated with two triggering components:

a cellular initiator in the cochlea, and a systematic component located in the central auditory system or in other brain centers that contributes to the long-term preservation of the pathology [46].
In summary, the theories underlying tinnitus cover all the pathway of the auditory system, as well as other systems that communicate with it. Due to the multiple abnormalities noticed in the patients affected by tinnitus, most of the theories proposed below are correlated to each other.

2.2.1. Pathophysiology in the peripheral auditory system

The peripheral auditory system is the outermost region that is normally affected by some pathophysiological conditions that leads to tinnitus. The abnormalities in the peripheral auditory system can be:

- Spontaneous otoacoustic emissions (SOAEs): the outer hair cells can sometimes produce small sounds due to their electromotile activity, even if the cochlea does not have any problem. However, this cannot be fully considered as a tinnitus trigger because the SOAEs can normally be cancelled via aspirin, which does not determine a decrease in the tinnitus loudness [53][17];

- Increase in the endocochlear potential: in order to ensure accuracy and efficiency in the acoustic-electrical transduction, the potential inside the cochlea must be kept as constant as possible. The outer hair cells are responsible for this, since with their electromotility they open and close the ion channels, regulating the concentrations of K^+ and Ca^{2+} inside and outside the cochlea. Hence, when the outer hair cells are damaged or malfunctioning due to e.g. a noise trauma, they tend to open their Ca^{2+} channels less frequently; as a consequence, Ca^{2+} ions start accumulating inside the cochlea leading to an increase in endocochlear potential and to the depolarization of the hair cells; in particular, the depolarization of the inner hair cells determines the release of the glutamate, which in turn leads to the depolarization of the cochlear fibers, and so to the aberrant excitation of the auditory nerve and to spontaneous activity in the cochlea [50];

- Edge theory: following this theory, tinnitus is generated when there is a dysfunction of the outer hair cells only in their basal part of the organ of Corti, while the apical is perfectly working. The poor functionality of that side determines spontaneous activity in the "edge area", which is the area in between the two sides of the organ of Corti [53][50].

- Discordant theory: according to this theory, when the cochlea is subject to an intense noise, excessive drug injection, or infections, its outer hair cells in the basal membrane are the first to be damaged. Tinnitus is a consequence of the "discordant" condition of the outer hair cells and the healthy inner hair cells: when it moves, the tectorial membrane of the damaged outer hair cells hits the stereocilia of the inner hair cells, leading to an increase in their depolarization; the neurons in the dorsal cochlear nuclei are stimulated by the higher depolarization rate of the inner hair cells, and they increase their firing rate as well. Due to this reason, the hyperactivity in the DCN is one of the main evidence in people suffering from tinnitus. Moreover, the reduced motility of the outer hair cells induced by the damage could decrease the precision in transduction of the inner hair cells, leading to the possibility to phantom sound inputs [53][17][50][40];

- Altered ensemble spontaneous activity (ESA) of the auditory nerve: the ESA measures the sum of the spontaneous activity of the nerve fibers of the auditory nerve. When guinea pigs and cats have been exposed to salicylate (ototoxic agent), a change in the spectrum associated to the ESA has been noticed, suggesting that the auditory nerve could play a key role in tinnitus generation. In particular, the central auditory system could interpret a modification from the normal random activity of the auditory nerve fibers to a more synchronous one as an incoming stimulation from the cochlea; therefore, due to that, high auditory centers could induce phantom sound perception [104][105].

2.2.2. Pathophysiology in the central auditory system and predictive coding model

Several physiological phenomena consolidated by experiments regarding the involvement of regions in the central auditory system in the perception and maintenance of the phantom sound are associated to the following solutions:

- Hyperactivity of the DCN: neuroplastic changes in the DCN are the consequence of damages to the outer hair cells caused by ototoxic agents or noise-induced trauma. The reduced efficiency of the outer hair cells decreases the electrical inputs conveying to the DCN. As a consequence, the auditory system has to increase its gain to compensate, leading to the disinhibition and consequently to the increased spontaneous activity of the DCN.
  This hypothesis arose after several experiments conducted on hamsters that were administered with cisplatin, a ototoxic substance that induces hearing loss and tinnitus. Cisplatin gradually damaged the outer hair cells of the hamsters and, after several doses were injected, the hamsters' DCN exhibited hyperactivity with a level depending on the severity of the cochlear lesion [104][17].
  Subsequently, the hyperactivity engages higher regions of the central auditory system communicating with the DCN, such as the inferior colliculus and the auditory cortex. It has been demonstrated that the hyperactivity induced by noise-induced trauma is not equally distributed all over the tonotopic maps of the central auditory regions, however it is more evident in those areas which are associated to the sound frequencies covered by the intense noise [42];

- Abnormal bursting firing rate and synchrony: in different animal experiments after noise, salycilate, or cisplatin body exposure increased bursting activity (i.e. a pattern characterized by the generation of sequences of action potentials followed by long quiescent periods) has been noticed in the fusiform cells of the DCN and in the interior colliculus, as well as an increase in synchronous activity (i.e. the simultaneous generation of action potentials in neurons belonging to the same neural network but to different part of the central auditory system). The bursting firing rate instead increased immediately after exposure, but then after few hours it returned to normal values [42][109];

- Maladaptive neural plasticity: it refers to the ability of the neurons in the central nervous system to alter their synaptic connections when a peripheral damage happens. Indeed, in tinnitus the nervous cells in the central auditory system which are subject to a lack of inputs (e.g. due to a cochlear damage), try to reorganize themselves in order to restore the previous neural network, and by doing this they introduce aberrant connections which can determine the perception of a phantom sound [50][17];

- Reorganization of the tonotopic map in the auditory cortex: experiments conducted both on animals and humans have demonstrated that the tonotopic map present in the auditory cortex of the tinnitus sufferers contains a shift in the location of the neural regions associated with the frequencies around the tinnitus pitch (as visible in Fig.2.3a). The shift amplitude was found to be proportional to the strength of tinnitus [42][84];

- Cross-talk theory: cross-talks refer to artificial synapses that may form between auditory nerve fibers when a cranial nerve is damaged. The generation of new synapses alter the auditory nerve circuits, and can lead to the manifestation of phantom sounds. These new neural circuits can develop due to nerve compression caused by blood vessels or tumors. The forces generated by those non-neural structures over the nerves can deteriorate the myelin sheath that covers the nerve fibers, consequently inducing ephaptic couplings between them. This theory is supported by the fact that a neurovascular decompression surgery results in significant improvements in tinnitus [53][17].

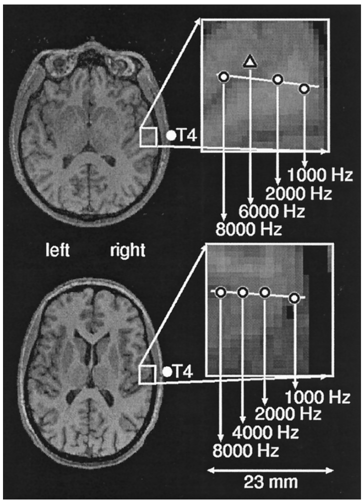
One of the most interesting and complex theory that aims to explain several neurological conditions such as tinnitus is the *predictive coding model*. According to the predictive coding, the brain is continuously updating a mental model of what happens in the environment, based on the sensory inputs it receives. Whenever an external stimulus is presented, the brain makes a comparison between the stimulus and the model elaborated from previous beliefs. When the stimulus differs from the model, a mismatch called prediction error is identified. The brain is so intelligent that is able to recognize when a prediction error is due to an important environmental change or noise. In the first case, i.e. when the prediction error is sufficiently reliable and is not incredibly distant from the boundaries of the model, the latter is updated. Before the final update however, the environmental signal must pass through several central processing levels: each level deals with beliefs that are considered priors in the level just below. Therefore, the final perception is dependent on a continuously optimized model.

In the case of tinnitus, the predictive coding model explains that the brain contains some problems in its central processing levels because it is not capable anymore to distinguish useful inputs from noise. Indeed, the precision in the prediction errors may enlarge for some reasons and also spontaneous activity in the auditory system (which normally is not a problem since the prediction errors elicited are too far from the model) can generate a prediction error that can update the generative model, introducing a phantom sound [50][60].

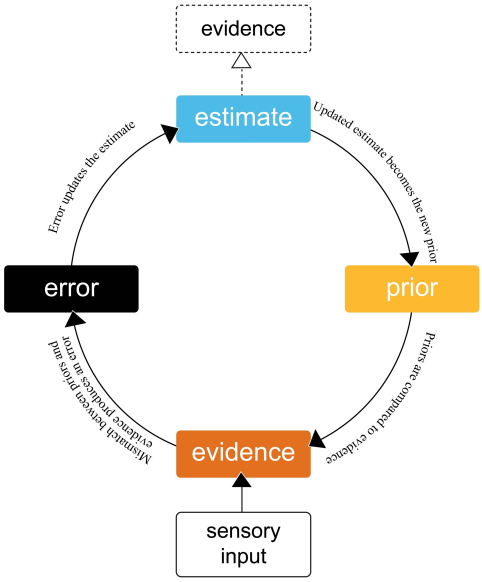
2.2.3. Roles played by non-auditory brain regions

Even if the main changes occur in the auditory system, other structures such as the somatosensory system, the limbic and autonomous nervous system seem to play a significant role in tinnitus.

Due to the proven direct communication between the *somatosensory system* and the dorsal cochlear nuclei



(a) Comparison between the tonotopic map of a left ear tinnitus sufferer (above) and the one of a person belonging to the control group (below) in a research study. The tinnitus frequency location is represented by the triangle in the upper figure [84]



(b) Scheme describing the hierarchical organization of the predictive coding model. The prior belief is represented by the estimate, which serves as an empirical control for the evidence and the sensory input. The prediction error is generated by the comparison between estimate and evidence, and, when the it is precise enough, it updates the estimate determining a new empirical prior. The loop is repeated until the prediction error is minimized [60]

through the medullary somatosensory nuclei, any somatosensory stimulation could be a cause of tinnitus modulation. Abrupt head, neck, or limb movements, whiplashes, temporomandibular-joint syndrome, etc. can all induce electrical stimuli that convey to the DCN and disinhibit it determining an abnormal spontaneous activity. Inputs originating in the trigeminal, vagal, facial nerves can all be considered sources for tinnitus manifestation, due to their interaction with the auditory system [53][49].

The *limbic system* is composed of both cortical and subcortical regions which are responsible for memory, emotions, and attention, and have nervous branches which interact with the auditory system. It is involved in the emotional responses derived by significant acoustic stimuli; in the tinnitus case, it is proven to be the main responsible for the manifestation and modulation of its distress component. In various animal and human studies it has been noted an abnormal activity in the amygdala, a region of the limbic system considered to be the final step for the elaboration of tinnitus-related discomfort. Nodes of the "tinnitus-related distress circuits" are also the frontal part of the cingulate cortex, the orbitofrontal cortex, and the anterior insular cortex, areas that have exhibited intense alpha activity in patients affected by tinnitus distress [121]. All these regions seem to be accompanied by neuroplastic changes once tinnitus originates [42]. Moreover, neuroimaging have revealed the activation of hyppocampal and parahyppocampal regions for the memorization process of a persistent sound like tinnitus [73].

Finally, even the autonomic nervous system is believed to be influenced by tinnitus, however there have not been sufficient investigations to draw significant conclusions [122][50].

2.3. Currently available treatments for tinnitus

As it has been explained in the previous chapter, it is not possible to define a unique cause or physiological mechanism associated with tinnitus. On the contrary, several abnormalities in different areas of the human body have been noticed in tinnitus patients. This is the reason why it has not been discovered a solution yet that can be considered effective in treating tinnitus for every single person, especially with respect to the non-pulsatile tinnitus.

In any case, before defining a treatment it is necessary to undergo clinical tests to estimate tinnitus loudness and annoyance and to identify the degree of hearing loss and the possible etiology and symptoms [114].

The treatments of tinnitus can have two different goals. There are therapies aiming to modulate tinnitus and to suppress it such as drug treatment and electrical/magnetic stimulation, while others focus more on the psychological consequences like distress, annoyance, and insomnia; in this category there are music therapy, counseling, massages, etc [118].

In this chapter all the possible treatments tested are going to be examined, but most of the attention is paid on those which are considered the most innovative and promising. According to this, two separate sections are dedicated to electrical and multi-modal stimulation.

Starting with *pharmacotherapy*, although several have been experimented, there are no drugs which have been definitely approved either in Europe or in North America for the treatment of tinnitus [7]. Even if they have demonstrated to be beneficial in a significant number of trials, the main problem of drugs intake is that, once the therapy is stopped, the tinnitus level returns as before the treatment or even worsens. This is the case of nortrypline, amitritlynr, alprazolam, clonazepam, acamprosate, and oxazepam. Lidocaine administered intravenously is the one that showed the most promising effects; however, this drug, which reorganizes the neurons in the right temporal lobe where the auditory association cortex is present, induces often side effects and therefore cannot be licensed. Aspirin is a common remedy for tinnitus caused by SOAEs, and antidepressants may be used when tinnitus induces an emotional factor [53][114]. Finally, in a clinical trial a cocktail made of Deanxit and Rivotnil has been tested, with a modest result in terms of tinnitus annoyance reduction [78].

In conclusion, due to the restricted group affected positively by each drug, a patient who undergoes pharmacotherapy must be conscious that he is going to test several medicines before finding an effective one that ultimately will reduce tinnitus loudness moderately [25].

A second common treatment adopted in the circumstance in which tinnitus provokes annoyance and stress is *counseling*. This is a therapy which cannot ensure any reduction in tinnitus loudness, but can help to induce habituation. The cognitive and behavioural therapy aims to delete all the negative thoughts behind tinnitus, e.g. by telling the patient that his stress is not going to raise and that he should avoid situations in which tinnitus loudness is perceived as maximal. At the same time, the therapist proposes visual and acoustic stimuli which distract and relax the patient [114][118]. A similar counseling approach is called tinnitus retraining therapy (TRT). It combines counseling with sound therapy at low intensities. By interacting with the limbic and autonomic nervous systems, the TRT focuses on the assumption that tinnitus is just an adverse effect correlated to the normal brain activity and therefore is something not to be worried about.

Unfortunately, counseling cannot ensure long-lasting effects after treatment and also it requires often more than one year to show evidences of improvement [53][114].

Pulsatile tinnitus can always be related to a physiological alteration and therefore, once detected, it can be properly treated. Patients who have tinnitus associated with problems to the cervical spine or shoulders can try *massage* and *stretching* as first remedies that have shown significant improvements; the body parts involved are the neck and the muscles of mastication [118].

When the tinnitus is caused by nerve compression, a *surgical* procedure is performed in order to reduce the pressure of the blood vessel on the nerve. This approach has shown good results, but the number of patients involved was too low to draw meaningful conclusions. Surgery has been also tested on patients suffering from non-pulsatile tinnitus. In the past, cochlea or auditory nerve removal was considered to be an effective solution. The outcomes were significant in reduction or elimination of tinnitus, but the main side effect of permanent hearing loss did not make it applicable.

Moreover, cochlear implantation has led to a significant improvement in 86% of patients. However, its benefits are restricted to a subgroup of people suffering from bilateral hearing loss[114][7].

Another valuable treatment for people suffering from hearing loss are *hearing aids*. It is considered as a form of sound therapy: indeed, hearing aids are used to amplify both the sounds coming from the environment and the human voice. They are therefore effective in masking the phantom sound and to focus the attention on something else. Due to this double effect and the absence of relevant drawbacks, it is the first treatment suggested for people suffering from hearing loss. Nevertheless, They are not suitable in case the tinnitus pitch is higher than 8 kHz because of device limitations in high-frequency amplification and also they do not help in quiet conditions such as during sleep [53][50][118][114].

Even though it has been criticized in the past, *neurofeedback* has shown promising results in the newest studies. This therapy examines the neuronal activity of a particular cortical area via signal-processed EEG recordings and returns a visual or auditory feedback to the patient. Exploiting the concept of operant conditioning, neurofeedback aims to make the neuronal activity directly controllable by the patient rewarding him when desired brain changes are obtained. However, the heterogeneity of the experiments conducted until now makes neurofeedback still under investigation [47].

Already used for chronic pain suppression, nerve and tissue regeneration, *laser therapy* has been evaluated also for non-pulsatile tinnitus. In this technique, the light emitted by diodes is directed to the tissue of interest, by which it is absorbed causing different biochemical reactions. Depending on the laser power, two laser therapies can be distinguished, and both of them have been experimented as tinnitus treatments. The Tinnimed device was used in a study to perform low-level laser therapy (LLLT) to induce athermic stimulation in the inner ear (see Fig. 2.4a). The laser emitter was positioned in the external auditory meatus so that a laser beam of 5 mW power could penetrate the tympanic membrane and hit on the cochlea. Mixed results have been obtained within all the LLLT trials regarding tinnitus loudness; moreover, the effects seem to decrease gradually once the treatment is stopped [90] [91].

The other possibility is to use medium-level laser therapy (MLLT, Fig. 2.4b), in which the device has a power of about 450 mW, able to ensure a laser energy up to 80 times bigger than the one in LLLT. The targeted part was the cochlea of the ear in which tinnitus was perceived as more intense. Unfortunately, the MLLT has not lead to any significant improvement [31][7].

Surprisingly, only one clinical trial has been conducted to assess the efficacy of a treatment based on *ultrasound*. This can be explained by the fact that ultrasound can be annoying at low doses and a source of hearing damage at high levels [88]. In the ultrasound therapy mechanical vibrations normally around 1 MHz are directed to the targeted area inducing oscillations of its smaller particles that can have several effects depending on the pattern of the sound wave. Therapeutic ultrasounds are used in various applications such as lithotripsy, cataract treatment, tumour removal, wound healing, etc. Unfortunately, this technique seems not to be beneficial for tinnitus: even though in the preliminary study some good outcomes emerged, none of the 40 participants subject to a low-level ultrasound therapy applied over the mastoid bone experimented a meaningful relief [100][13].

Also the *hyperbaric oxygen therapy (HBOT)* does not seem to be a reliable tinnitus suppressant, mainly due to its serious adverse effects encountered in other applications of this technique. The HBOT consists of the exposure to 100% oxygen in a pressurized room or tube (P > 1 ATA). If the exposure time is prolonged enough, multiple organs can suffer from oxidative stress and oxygen toxicity. In an experiment patients suffering from chronic tinnitus underwent HBOT at 2 ATA for 90 minutes for 10 sessions. Initially, the outcomes have been interesting in terms of decrease in tinnitus perception, but they have started worsening some months after the treatment [118][70].

(a) Low-level laser therapy performed via the Tinnimed device [97]

(b) Lasotronic device used for medium-level laser therapy in a clinical trial [31]

Figure 2.4: The two possible laser therapies experimented for tinnitus

Due to its positive results, the non-invasivesess and the complete absence of side effects, one of the most successful and used treatment for tinnitus is the *sound therapy*. One form of sound therapy has been already presented, the passive sound amplification obtained by the use of hearing aids. Passive amplification however is effective only in presence of an external noise (either environmental or in form of human voice) that can mask tinnitus. The other option is to use active amplification via sound/noise generators, especially useful in quiet situations. The generation of particular sound/noise patterns does not extinguish the phantom sound, but it may decrease tinnitus loudness and distress, as well as help to habituate [25]. For all these reasons sound therapy is currently being investigated in combination with other stimulation treatments, as will be explained in the last section of this chapter.

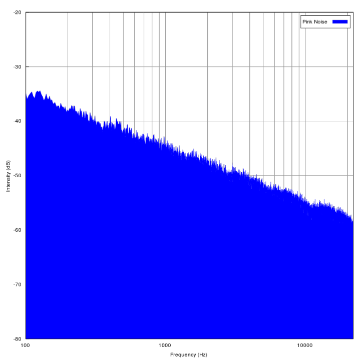
A great amount of sound therapies are available and have been tested. Most of them require a preliminary audiometry to detect the tinnitus frequency pitch and intensity of each patient in order to adjust the sound level and modify properly the sound frequency spectrum.

The most simple sound treatment is represented by natural sounds. Natural sounds such as rain, wind, streams are used especially during sleep to decrease the strength of tinnitus-related neuronal activity within the auditory cortex and to induce patient relaxation [53].

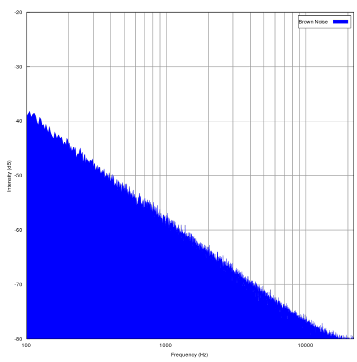
Employed because of their unpredictable pattern, "fractal tones" induce passive listening which can help in tinnitus habituation. The "fractal tones" therapy consists indeed in the temporal random repetition of groups of frequencies included in a chosen frequency band. All the participants in a study have exhibited remarkable and long-lasting results as regards tinnitus distress reduction, demonstrating that a sound therapy based on unpredictability may be promising [96][115].

The concept of unpredictability may also explain the long-lasting effects of the broadband (BB) noise therapy. A noise is defined broadband when its frequency spectrum contains all the range of audible frequencies (around 20 Hz-20 kHz). Depending on the intensities of each frequencies, a broadband noise may be:

- White noise: when the frequencies have all the same intensities (S constant);
- Pink noise: when the power spectral density is inversely proportional to the frequency (S ~ 1/f). It means that all the audible frequencies are present, but the lower are the louder ones;
- Brown noise: it is similar to pink noise, but with even more emphasis on the low frequencies (S ~ $1/f^2$) [12];
- Blue noise: when the spectral power is proportional to the frequency (S ~ f). therefore, it is the opposite of pink noise [14][24].



(a) Frequency spectrum of pink noise. The power density is subject to a constant decrease of 3 dB/octave



(b) Frequency spectrum of brown noise. The slope is steeper than the pink noise one (-6 dB/octave)

Figure 2.5: Examples of noise colours used in sound therapy [2]

Sound therapy based on broad band noise has been tested in numerous trials. Even if the results are modest in terms of tinnitus reduction, it has demonstrated to be more effective than counseling and natural sounds therapy, when the BB noise levels are just below the tinnitus intensity level [36].

The generation of broad band noise is part of a tinnitus-specialized therapy called Neuromonics tinnitus program used for people who have a certain degree of hearing loss. Neuromonics combines a behavioural therapy to a music therapy (relaxing music chosen by the patient) containing a audiometrically-tailored BB noise component in which the frequencies associated with the hearing loss (and so the tinnitus ones) are amplified. Neuromonics have had a high clinical success (86 % patients have met the minimal requirements for positive outcomes) but the trials conducted are not sufficient for a final judgement of the therapy [54].

Opposite to the concept of BB noise is the one of narrowband (NB) noise, in which only a small group of audible frequencies are amplified. In the case of tinnitus, NB noise encompasses the frequencies matched to the tinnitus octave. Under this treatment there is the theory that stimulating the tinnitus-related frequencies can reduce the increased spontaneous activity encountered in the auditory cortex of the people suffering from tinnitus. Acoustic Coordinated Reset (CR) neuromodulation and Otoharmonics Levo systems fall under this category of treatments. The first one is based on the temporally random presentation of sinusoidal, NB tone ensembles with frequencies around the tinnitus one. Otoharmonics Levo system delivers via earbuds pitched-matched NB sounds. Nevertheless, neither of the treatments have shown significant outcomes in all the trials [67][51][59].

Another possibility is tailor-made notched music in training (TMNMT). TMNMT is a tinnitus treatment based on the presentation of a pleasant music spectrally modified via a notch filter with a stopband covering the tinnitus pitch realized by audio technology. The basic principle of the TMNMT is the idea that the hyperactivity in the areas of the auditory cortex coding the tinnitus frequencies can be decreased via the lateral inhibition (i.e. the inhibition of a neuron activity subsequent to the excitation of a neighboring cell [9]) from the edges of the notch. The experiments have revealed noticeable improvements in tinnitus loudness, but not particularly in distress reduction [48][89][111].

Eventually, a sound treatment based on a phase-shift mono-frequency can be performed. Usable in case of monotone tinnitus, it is realized by periodically shifting the phase of a sinusoidal tone having the same frequency as the tinnitus one. Nothing can be said about it since too few studies have been conducted [112].

Due to its mild effects but the positive aspects and the possibility to induce different physiological changes, sound therapy does not seem to be the definitive approach for complete tinnitus healing but is suitable for being included in a multi-modal treatment, which currently seems to be the major focus of scientists.

2.3.1. Approaches based on electrical stimulation

As it has been explained before, sound therapy and cochlear implants, which are the most promising treatments, present limitations: the first one can only lead to partial tinnitus suppression and from a physiological point of view is not able to prevent deafferentiation of the auditory nerve that is one of the possible causes of tinnitus; on the other hand, cochlear implants can be very effective and present a high percentage of success in tinnitus removal, but they are only applicable for people who have significant hearing loss. Therefore, another solution is being explored nowadays that can avoid these issues: electrical stimulation.

Electrical stimulation has been taken into consideration for 200 years, but there have been several factors that hindered the scientific community to clinically approve any protocols or devices for electrical stimulation valid for tinnitus sufferers. As already analyzed in a previous chapter, above all these factors there is the lack of a defined scientific explanation for tinnitus that could guide technological development. Secondly, the safety aspect is really important, especially in long-term stimulation. Further, the stimulus parameters tested for tinnitus are not uniform; their range is too large and not optimized. Finally, there are not many electric stimulators designed specifically for tinnitus; as a consequence, in all the studies performed right now only stimulators for pain management or customized devices for research purposes have been used [130][131].

DC stimulation has been generally applied to deliver constant low direct current in the ear canal or with transcranial stimulation but not in the inner ear or for nerve stimulation because it may promote bone growth or neurotoxicity [131].

Mielczarek et al. tested the so called *"hydrotransmissive stimulation"*. It consists of the delivery of a voltage-driven, rectangular, and positively polarized current through a silver electrode electrically connected to the ear canal due to the insertion of a saline solution within it. The cochlea is directly stimulated due to the positioning of the cathode in the forehead. The treatment was based on 4 minutes DC stimulation per day, 3-4 days per week for 30 days. The device used was a custom-made one powered by four 1.5 V batteries. The stimulation parameters applied were adjustable and the stimulation duration was proportional to the stimulation frequency, which in turns depended on the tinnitus pitch (F = [250, 8000] Hz). In one patient, for instance, the parameters were: stimulation duration t_S = 2 mins (and 2 mins pause), input voltage amplitude V_{IN} = 3 V, current intensity I = [0.15, 1.15] mA, and stimulation frequency F = 250 Hz. The outcomes have indicated a complete tinnitus suppression for 1/3 of the patients, but only 10 % of them maintained the benefits after 90 days post stimulation [81].

Transcranial DC stimulation (tDCS) is a even less invasive technique in which both the electrodes are placed over the scalp of the patient. tDCS seems to have opposite neurophysiological effects depending on the polarity of the current: anodic stimulation induces neurons' depolarization while cathodic leads to their hyperpolarization. Analyzing the results of the studies, the most effective seems to be the anodic one. Depending on the width of the area to be excited (that does not mean that the less wide one is more effective since the tinnitus may have several causes associated to different locations), tDCS has two anatomical targets: the left temporoparietal area (LTA), which ensures a more widespread stimulation, and the dorsolateral prefrontal cortex (DLPFC) that is associated with a more precise but localized stimulation. The cortical and subcortical areas underneath the LTA affected by stimulation includes the auditory cortex, the amygdala, and hippocampus, which are all involved in tinnitus perception [108]. DLPFC seems to be related to tinnitus annoyance since it contains neurons that control auditory memory and attention.

The first experiments conducted on chronic tinnitus patients have revealed moderate results. For instance, in their clinical study, Joos et al. delivered a 20 minutes constant current of 1.5 mA and 2 mA via a 35 cm^2 active electrode over the left or right auditory cortex and a return one placed on the contralateral arm. Although the treatment seemed not to be particularly effective (only 13% patients improved their condition significantly), the researchers have noticed that the success was depending on the stimulation parameters, especially on the current amplitude [64]. Therefore, the goal of the research on tDCS for tinnitus has shifted to the determination of the correct stimulation parameters. Vanneste et al. have determined which are the most effective stimulation parameters and therapy duration for a long-lasting DLPFC tDCS: current intensity I = 1.5 mA, stimulation duration t_S = 20 mins, and therapy duration $N_{sessions}$ = 6 (with a pause period of 3-4 days per session) [107]. Instead, the best parameters in case of tDCS applied over the LTA have been investigated by Shekhawat et al. (79% patients who received benefits in tinnitus loudness experienced long-lasting effects) and seem to be the following: current amplitude I = 2 mA, stimulation duration t_S = 20 mins, and therapy duration $N_{sessions}$ = 6 (with a washout period of 3-4 days) [108].

Afterwards, the effectiveness of tDCS has been compared to the one of a relatively new technology developed by Soterix based on a high precision and small depth electrical stimulation, called *High-Definition tDCS (HD-tDCS)*. HD-tDCS is a type of tDCS through which small regions of the central nervous system are stimulated via an array of electrodes applied over the scalp. In contrast to conventional tDCS, which uses large sponge electrodes, HD-tDCS relies on small gel-based electrodes [77]. Shekhawat et al. performed HD-tDCS on chronic tinnitus patients using 4 ring electrodes with 12 mm radius targeting the LTA and the DLPFC. When the optimal stimulation parameters found by Shekhawat et al. and Vanneste et al. (I = 2 mA and t_S = 20 mins) have been applied, a significant transient improvement for both tinnitus loudness and annoyance has been reported in 78% of the patients after 1 week of treatment, which was higher than previous tDCS trials [66].

Unfortunately, if all the studies are taken into account, only about 39.5% of patients have responded to tDCS, with a mean tinnitus intensity reduction of 13.5%, which is not clinically significant to draw positive conclusions [25].

Recently, the stimulation pattern of tDCS has been varied in order to verify if a more effective therapy based on the same principle (two electrodes applied over the scalp) could be found. In particular, interesting outcomes have been shown after the application of so called *transcranial random noise stimulation (tRNS)*. In tRNS a weak alternating current characterized by a spectrum with random frequencies included in the range from 0.1 to 640 Hz is delivered transcranially. An explanation that has brought the scientists to assess tRNS for the auditory cortex is that *"... there is a brain state-dependent effect of tRNS similar to what has been seen in tDCS, meaning that adding a noise to an already present hypersynchronization of the auditory cortex in tinnitus patients might induce a disruption of the ongoing hyperactivity, ultimately resulting in a transient suppression of tinnitus. In contrast, resting state activity in the auditory cortex of a healthy subject represents a noise-like signal and adding a noise might therefore result in an increased synchronization or even the absence of any effect."* [65]

tRNS has demonstrated to be very promising. Indeed, when compared to both tDCS and tACS (i.e. transcranial alternating current stimulation) with the same stimulation conditions (stimulation duration t_S = 20 mins, current amplitude I = 1.5 mA) except for the frequency (in tACS 6-13 Hz, in tRNS 0.1-100 Hz), it has revealed to be more effective both in terms of tinnitus intensity and annoyance reduction [120]. Furthermore, De Ridder et al. have discovered that low-frequency (0.1-100 Hz), high-frequency (100-640 Hz), and wide-band (0.1-640 Hz) tRNS do not exhibit the same results. Indeed, although both the first two are similar in treating loudness, only low-frequency tRNS is beneficial for tinnitus distress. Instead, wide-band tRNS has not shown any significant effect [65]. Moreover, long-term tRNS (10 mins sessions in the auditory cortex for a 4 weeks treatment) have demonstrated not to generate adverse reactions and at the same time to lower annoyance (but not loudness) [82].

The analysis of the trials conducted on tRNS has led to the formulation of the potential advantages of this treatment. Firstly, unlike tDCS it does not require conduction of parallel studies to assess the excitability changes since it includes an implicit charge-balanced mechanism; secondly, the treatment does not cause particular annoyance due to the lack of a net current, and so it is more tolerable than tDCS; lastly, since it causes large neurobiological changes, it does not require a precise stimulation or a well-defined electrode design to engage a specific region of the brain (e.g. TMS, explained below, requires a high target focality to affect a precise zone) [72].

A technique that is based on a similar principle to tDCS is *transcranial magnetic stimulation (TMS)*. TMS has been used since the '80s for a variety of disorders, including depression and anxiety, and many studies have been conducted for tinnitus, too. In TMS, a wired coil is positioned over the head of the patient. When a brief electrical current is applied, it starts flowing through the coil generating a magnetic field that in turn due to electromagnetic induction generates an induced current in the brain. Subsequently, depending on the frequency, duration, and intensity of the magnetic field, the current starts provoking action potentials in the neurons, leading to increased or reduced neural activity in some cortical regions. TMS compared to tDCS guarantees a better spatial and temporal resolution and has well defined protocols, however it is not cost-effective and may be linked to undesirable effects such as lower mobility. In the pilot study conducted by Lefaucheur et al. tinnitus has been temporarily reduced in 50% of the cases by using repetitive 40 minutes-sessions of TMS with biphasic pulses repeated with frequency F = 1 Hz (2400 pulses per session) applied over the auditory cortex. However, an increased hyperacusis has been noticed as a side effect in 50% of the people [85][66].

Together with DC stimulation and TMS, another non-invasive approach that has been and is currently being tested is called *transcutaneous electrical nerve stimulation (TENS)*. Originally used for pain relief, TENS consists of the application of electrical pulses through the skin via electrodes positioned in such a way that it leads to the activation of a specific nerve. The numerous advantages of TENS including complete non-invasiveness, patients' partial self-management (stimulation parameters are normally adjustable by the patient, but the therapy must be supervised by a clinician), absence of evident side effects (only paresthesia), rapid onset and offset, and cost-effectiveness (compared to drug therapy or others) have encouraged its experimentation for several other applications such as tinnitus [63].

In the attempt to suppress tinnitus, TENS devices have been used so far to target two nerves: the cervical spinal nerve 2 (C2) and the vagal nerve.

In the first case, two electrodes are placed bilaterally in the neck, precisely in the left and right C2 nerves dermatomes. Some studies have demonstrated that there is a junction between the somatosensory and the auditory systems represented by the DCN. Since there are branches of the C2 nerve that form synapses in the DCN, its electrical stimulation generates action potentials in the neural cells of the DCN. In turn, once activated, the DCN sends inhibitory signals to the higher regions of the central nervous system, which may alter their hyperactivity noticed in tinnitus patients. In a study conducted by Vanneste et al. TENS was applied for 20 minutes (and 20 minutes of sham stimulation); the first 10 minutes biphasic rectangular pulses were delivered, with a pulse width W_P = 250 μs and a frequency F = 6 Hz; in the other minutes only the frequency was varied, to the level F = 40 Hz. The current intensity was increased until paresthesias was perceived, and then slightly reduced (most of the patient were stimulated with I = 30 mA). Eventually, the experiment has not brought to a desired conclusion: indeed, only 17.9% of the patients experienced a significant tinnitus reduction, with few cases of complete suppression. Furthermore, the effects have persisted only during stimulation [113].

On the other hand, the transcutaneous stimulation of the vagal nerve can be realized by placing two electrodes in the external ear. Indeed, multiple anatomical structures in the outer ear contain terminal branches of the vagal nerve. One of this structure is the tragus, which is innervated by the auricular branch of the vagus nerve (ABVN). Driven by the theory that vagal nerve stimulation may induce neuroplasticity and reduction in tinnitus annoyance by modulation of emotion-related neural regions, Kreuzel et al. stimulated the ABVN through two small titanium electrodes placed over the tragus. The patients were instructed to use the stimulator for at least 4 hours per day under the following conditions: period of active stimulation T_{ON} = 30 s, period of break T_{OFF} = 30 or 180 s (depending on the group the patients were belonging to), stimulation frequency F = 25 Hz, current amplitude I = [0.1, 10] mA. After around 6 months the therapy has not exhibited any significant improvement in tinnitus. In the researchers' opinion, the only plausible reason behind this may be that the transcutaneous electrical stimulation of the vagal nerve alone is not sufficient for treating tinnitus [71].

Two minimally invasive therapies have been also tried which interest the electrical stimulation of the cochlea: the *promontory* and *round window stimulation*.

The first one was realized by Perez et al., that used a transtympanic needle electrode and a reference electrode in the forehead. Biphasic charge-balanced, rectangular pulses were delivered with a current intensity up to 1 mA and two alternating frequencies F_1 = 100 Hz and F_2 = 1800 Hz for a stimulation time per session t_S = 30 mins (15 mins at 100 Hz and 15 mins at 1800 Hz), with 3 sessions per day. The treatment has been effective in 50% of the people in terms of decrease in tinnitus intensity, but the sound has returned as loud as before within 4 weeks after the stimulation has been stopped [94].

Wendel et al. instead performed an experiment for assessing the effect of the stimulation of the round window by using a ball electrode connected to a cochlear implant system. After a 3.5 years treatment based on biphasic charge-balanced pulses with amplitude I = [0, 3] mA and frequency F = [0, 100] Hz (both parameters adjustable by the patient) delivered for 4 hours per day, temporary relief was observed in all the three patients, of which only one benefiting from complete sound suppression [126].

Finally, a last type of electrical stimulators that has been tested is by means of percutaneous implants and deep brain stimulators. Even if in several cases they have shown great benefits especially with regard to tinnitus loudness, their high level of invasiveness limits their use to people who have such a high level of tinnitus that their quality of life is severely degraded.

The most invasive approach is *deep brain stimulation*, in which tiny electrodes are implanted deep in the brain via surgery. In this way, the electric field resulting from the current delivered through the electrodes is confined in a small cerebral region. Deep brain stimulation has been used to elicit the caudate nucleus and the DCN. Even if does not seem to be connected to the auditory system, the stimulation of the caudate nucleus has revealed positive effects in some cases. Cheung et al. applied a therapy in six patients based on voltage pulses setting the following parameters in the stimulator: voltage amplitude V = [0, 10] V, pulse width W_P = [60, 90] μs, frequency F = [150, 185] Hz, stimulation duration t_S = [60, 240] s. At the end of the study, 5/6 patients have experienced a tinnitus loudness modulation, beneficial in some cases and negative in others. Depending on the voltage amplitude set, the stimulation demonstrated several degrees of effectiveness, suggesting the need for further investigation to determine the best stimulation parameters for caudate stimulation [16].

At the same time, the dorsal cochlear nucleus may be a possible site for electrodes' implantation, due to its active part in the development of tinnitus. Studies have already been conducted on rodents but not yet in humans. Despite of the unclarity on the mechanism of deep brain stimulation, there is evidence that suggests that high frequency stimulation disrupts the abnormal electrical activity in the DCN. Therefore, convinced by this, Van Zwieten et al. implanted 50 μm electrodes bilaterally within the DCN of 10 rats and the high frequency stimulation delivered (bipolar monophasic pulses with pulse width W_P = 60 μs, current amplitude I = 100 μA, and frequency F = 100 Hz) has contributed to the suppression of their trauma-induced tinnitus [119].

A surgical procedure was also performed when Engelhardt et al. wanted to directly stimulate the auditory cortex (hence, not deep brain stimulation). Epidural electrodes were placed over the auditory cortex in patients suffering from unilateral tinnitus and a pulse generator in the chest to deliver a voltage-controlled bipolar stimulation (voltage amplitude V = 3 V, frequency F = 80 Hz, and pulse width W_P = 300 μs). After 4 months of stimulation, the amount of patients with significant tinnitus reduction were 56%, with some cases of great improvement; then, within the people that continued to use the implant for more than 1 year 40% were still feeling the benefits, both in tinnitus loudness and distress. Nevertheless, considering the overall benefits and drawbacks, the researchers have assessed cortical stimulation as not effective in treating chronic tinnitus relying on these therapeutic conditions [38].

Eventually, the anterior cingulate cortex was also tested as a site for brain stimulation once functional imaging has revealed its involvement in the neuronal network associated to tinnitus distress. After several TMS sessions applied on two patients with a high level of tinnitus distress, De Ridder et al. implanted electrodes bilaterally in the anterior cingulate cortex. Two different treatments were applied: 6 Hz (close to the 5 Hz used for TMS) tonic stimulation and burst stimulation consisting of 5 spikes of current amplitude I = 1.4 mA. The patient who did not respond to TMS did not get any benefit neither with tonic nor burst stimulation; on the contrary, the other patient, which was affected by a transient beneficial effect with TMS, has experienced a drastic improvement after 1 week of tonic stimulation; later, the improvements have increased even more when burst stimulation was delivered and have remained constant for 2 years. Hence, the fundamental findings of the two trials have been that cingulate stimulation does not work for all the severely distressed patients and that TMS may predict the effectiveness of the cortical implant (and thus may be used to avoid unnecessary implantations) [29].

2.3.2. Treatments involving multi-modal stimulation

The need for a tinnitus cure that can simultaneously decrease the annoyance and loudness of tinnitus permanently (or for a long period of time) has shifted the attention of the scientists to another concept that had never been explored before: multi-modal stimulation. The term multi-modal stimulation refers to the application of a combined therapy capable to stimulate simultaneously different areas likely to be involved in the tinnitus-related pathophysiology. Two types of multi-modal stimulation have been currently experimented:

electrical-electrical stimulation and electrical-sound stimulation.

A patient in which tinnitus was defined by both a pure tone and narrow band noise was subject to *double electrical stimulation* in an experiment designed by De Ridder et al. Epidural electrodes have been implanted over the second auditory cortex while afterwards TENS has been applied on the C2 nerve. Surprisingly, the pure tone component has been completely eliminated thanks to the cortical stimulation and the noise component has been significantly reduced due to the somatosensory stimulation of the C2 nerve. Furthermore, the efficacy of the therapy has been ensured for more than 5 years. In the end, the longstanding effects but also the unknown physiological mechanism should encourage scientists to further investigate this "bi-electrical" stimulation treatment. At the same time however, the optimism should not be exaggerated since cortical stimulation was demonstrated not to be effective in the majority of the patients [26].

The second multimodal approach that has been studied is the *combination of electrical and auditory stimulation*. Right now, electrical stimulation has been applied to three different nerves that are supposed to influence tinnitus: the C2, the trigeminal, and the vagal nerve.

Susan Shore and her team at the University of Michigan have designed a device ("Michigan Tinnitus device") that delivers at the same moment timed sounds and a moderate electrical current. The two stimuli travels along two different paths but they have the same generator, ensuring the possibility to be synchronized. The auditory stimulus (which is chosen based on the patient audiogram) is delivered via headphones while the somatosensory stimulation is realized through transcutaneous electrodes applied over two different locations: when positioned over the cervical spine, they activate the C2 nerve, whilst if sticked to the cheeks, they stimulate the trigeminal nerve [43]. Both nerves have indeed an impact on the neural activity of the dorsal cochlear nucleus, and convey pulses that may reduce its tinnitus-associated hyperactivity.

A conceptually similar device has been developed by Neuromod (see Fig. 2.6c), in which the electrical stimulation is conveyed to the trigeminal nerve endings through the use of a intra-oral device composed of 32 tiny transmucosal electrodes which must be kept in contact with the tongue (saliva is used as the conductive medium). The headphones and the intra-oral device are connected to a controller via bluetooth and wire, respectively.

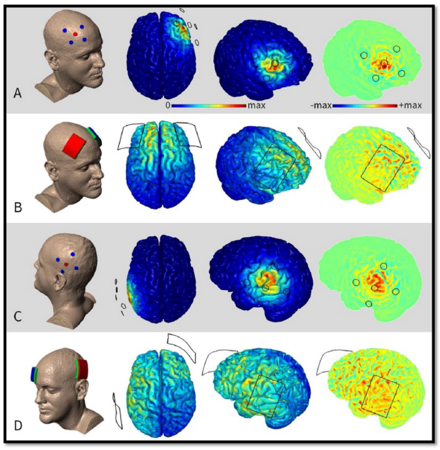
Subsequently, experiments have been conducted to assess the performances of the two devices. Firstly, Marks et al. have demonstrated the potential of the Michigan Tinnitus device: twenty patients used the device for 8 weeks, 30 minutes per day and 50% of them reduced meaningfully their tinnitus loudness and annoyance (with two cases of complete suppression) for up to 3 weeks after treatment [76]. On the other hand, the Neuromod device has been tested by D'Arsy et al. Biphasic anodic 17.5 μs wide pulses of variable amplitude have been delivered through the tongue of the patients every day for 10 weeks (stimulation duration t_S = minimum 30 mins) combined with white noise music and pure tones, and very promising results (44 patients have concluded the trial, 57% and 73% of them have improved significantly respectively in tinnitus distress and loudness) have proven the potential benefits of the device [52].

Eventually, the most interesting treatment in terms of outcomes seems to be the *vagal nerve stimulation paired with sound therapy*. Due to its incredible results seen in animal studies (100% tinnitus disappearance in a study on rats), several trials have been conducted. All of them involved the implantation of the lead electrodes beneath the neck, wrapped around the left branch of the vagal nerve because the right one has been demonstrated to convey towards the sinoatrial node with likely cardiac consequences. Moreover, all of them involved the same sound therapy, based on the generation of pure tones with random frequencies within a range excluding the tinnitus one. Indeed, the idea behind that stimulation is to shift the attention of the brain from the tinnitus by tuning cortical neurons to other frequencies. At the same time, VNS is known to act in several manners on the nervous system: it induces plastic changes in the auditory cortex through the release of neurotransmitters, improves the memory of associated events (and so, frequencies that are enhanced by the acoustic stimulation), and reduces the tinnitus-related anxiety by activating the parasympathetic nervous system [39][27].

Pushed by these possible implications, De Ridder et al. applied a therapy in which the electrical pulses of the VNS were synchronized to the music tones thanks to the communication between an external synchronization computer (that generates the tones) and an external stimulator (that receive the control signals coming from the computer). The electrical stimulation consisted on biphasic pulses, with amplitude I = 0.8 mA, pulse width W_P = 100 μs, and frequency F = 30 Hz. The therapy was applied on a chronic bilateral tinnitus patient for a non continuous period of 2.5 hours/day. After 4 weeks of treatment, the patient has experienced significant improvements both in terms of intensity of the sound perceived and distress, which lasted for 2 months without noticeable adverse effects. Then, a sham stimulation based on only acoustic stimulation was performed, which did not show any improvement on the patient, meaning that the multi-modal stimulation may be more beneficial [28].

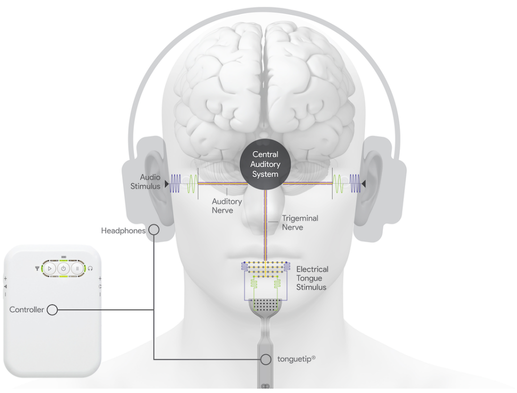
Subsequently, Tyler et al. tested the effectiveness of the therapy offered by a recently CE marked tinnitus device, called Serenity System (by MicroTransponder, Fig. 2.6d). The Serenity System is an evolution of the stimulation system used by De Ridder et al., in which the synchronization of tones and electrical pulses is ensured via the wireless communication between a computer and an implanted pulse generator through a wireless transmitter. The device has demonstrated to have promising long-term benefits when the same stimulation parameters of the study of De Ridder et al. have been applied: 15/30 patients implanted with the VNS have received clinically meaningful improvements during the first 6 weeks of treatment, and approximately 50% of them has maintained those effects after 1 year of stimulation [101][117].

Hence, VNS paired with sounds have demonstrated to deserve further investigation. The studies are currently addressed on optimising the stimulation parameters and the stimulation pattern (indeed, right now only tonic and burst VNS stimulation have been used), and at the same time to find anatomical locations which allow to stimulate the vagal nerve in a less invasive manner, in order to widen the population of treatable patients [24].

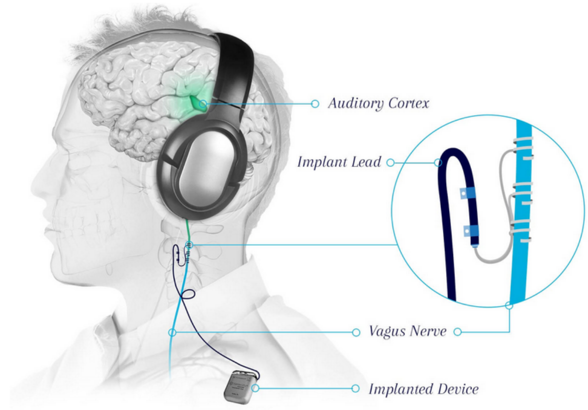


(a) Comsol simulation of the electric fields generated by respectively DLPFC HD-tDCS, DLPFC tDCS, LTA HD-tDCS, and LTA tDCS (from top to the bottom images) in the study of Shekhawat et al. [66]

(b) Transcoutaneous vagal nerve stimulator developed by Parasym (electrodes are clipped in the tragus region and a portable stimulator allows to select the stimulation parameters) [93]



(c) Multimodal stimulation device developed by Neuromod [19]



(d) Multimodal treatment based on sound therapy paired with VNS by MicroTransponder [80]

Figure 2.6: Examples of treatments based on electrical stimulation for tinnitus

3

Device specifications

3.1. General idea

Following the interesting results and studies presented in the last section of the previous chapter, the project focuses on the realization of a multi-modal stimulation device that can combine electrical with acoustic stimulation.

The device is intended for people that suffer from either unilateral or bilateral tinnitus and aims to reduce both their tinnitus loudness and annoyance.

In order to realize multi-modal stimulation, the device should act at the same time as an audio player and as a transcutaneous electrical nerve stimulator. As an audio player, the device has to be able to process an input audio file and to deliver its associated acoustic signals to both ears by connecting headphones to the audio channel of the device. At the same time, it has to generate one or two electrical signals with a particular and controllable pattern (that will be explained below), which have to be delivered in different locations in order to electrically stimulate nerves that communicate with the auditory system. This is possible by using electrodes connected to the different output channels of the stimulator.

The device must be used for several hours per day and has to allow the patient to perform his daily life without impairments. Therefore, it must be portable, battery-powered, user-friendly, and relatively lightweight.

The most innovative and interesting features of the device are the possible therapies. All of them have never been explored before. The first one combines electrical burst stimulation with pure tones having frequencies around the tinnitus one. The idea is that pairing a tinnitus-matched tone with a relaxing electrical vagal nerve stimulation will detach the associated arousal of the tinnitus, by taking away the paradoxical salience attached to the tinnitus tone. In this way, neuroplasticity could play a key role in modifying the neuronal connections and firing rates, inhibiting the activity of the neurons responsible for the tinnitus frequencies.

The second therapy is defined as "noisy pseudo-DC" stimulation, in the sense that the electrical signal that is delivered contains both a DC and a noise component, similar to what happens for the random noise stimulation. However, in this novel electrical pattern the noise is accurately selected and only low spectral components are present. In this embodiment, the noise stimulation is also paired with tinnitus-matched sounds. In this case, the attention of the brain should shift to frequencies other than the tinnitus one, increasing the firing rates of the related neurons in the auditory cortex, and contemporarily inducing habituation to tinnitus frequencies. In particular, the noisy character of the electrical stimulus prevents habituation to the lower frequencies, leading to an effective and long-lasting suppression of tinnitus.
The use of two different electrical waveforms coupled with the same acoustic stimulation will allow understanding which one of the two electrical stimulations is more effective in treating tinnitus.
Detailed information on the design requirements is explained in the following sections.

3.2. Device functions

Due to its role as a multi-modal stimulator, the device incorporates two products in one. It is a transcutaneous electrical nerve stimulator (TENS) because it delivers non-invasively through transcutaneous electrodes a specific electrical current through the tissue, in such a way that a particular nerve is stimulated. At the same time, the device acts as an audio player that processes an audio file and transmits a sound externally via an auxiliary tool (headphones or speakers).

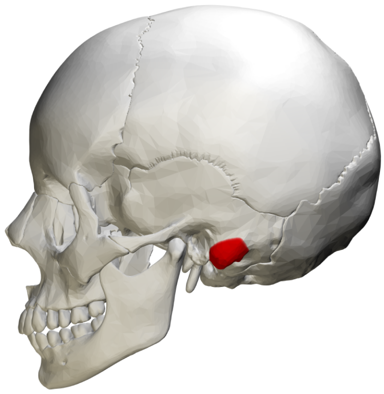
3.3. Stimulation sites

The device aims to stimulate several areas which are part or communicate with the auditory system.
Thanks to its function as a music player, the sounds produced cross the entire auditory system, from the outer ear to the central auditory centers. In particular, they stimulate the auditory cortex inducing neuronal activity in the portion of the tonotopic map associated with the more intense components of their acoustic spectrum.
On the other hand, depending on the location of the electrodes, the electrical stimulation may involve different nerves:

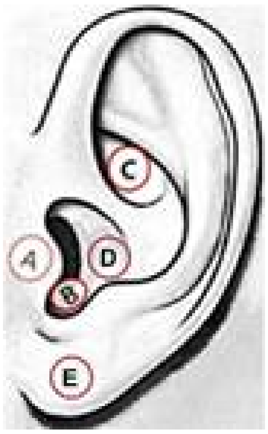
- Tragus and other locations of the outer ear: all the sites visible in Fig. 3.1b are targets for stimulation due to the proximity to afferent fibers of the vagal nerve and trigeminal nerve, called auricular branch of the vagus nerve and auriculotemporal nerve, respectively. The stimulation of afferent nerves is advantageous because the induced action potentials will spread towards the central nervous system without affecting peripheral areas and therefore inducing possible unwanted effects.
- Mastoid process: it is the posterior portion of the temporal bone, located behind the ear (Fig. 3.1a). The stimulation of the mastoid process may activate the C2 nerve through the lesser occipital and the great auricular nerves.

It is important that the device allows for bilateral stimulation: in the case in which the stimulator is used by a patient suffering from bilateral tinnitus, it has to ensure that both symmetrical areas of the body are stimulated in an equal manner at the same time. For instance, for tragus stimulation, the electrodes must deliver current simultaneously to both the left and the right tragus.

A possible electrodes-headphones design for tragus stimulation is proposed in Fig. 3.2. As can be seen, electrodes and earbuds are incorporated in one single component, that can be positioned in the ear and secured behind the helix via its upper portion. The earbuds deliver the sound while the electrodes, clipped on the tragus, perform an electrical bipolar stimulation. The wires must be connected to the output channels of the stimulator.



(a) Anatomical position of the mastoid process [127]



(b) Locations of the ear that could be involved in the electrical stimulation: tragus (A), cymba conchae (C), cavity of conchae (B and D), and lobule (E) [79]

Figure 3.1: Multi-modal stimulation: stimulation sites

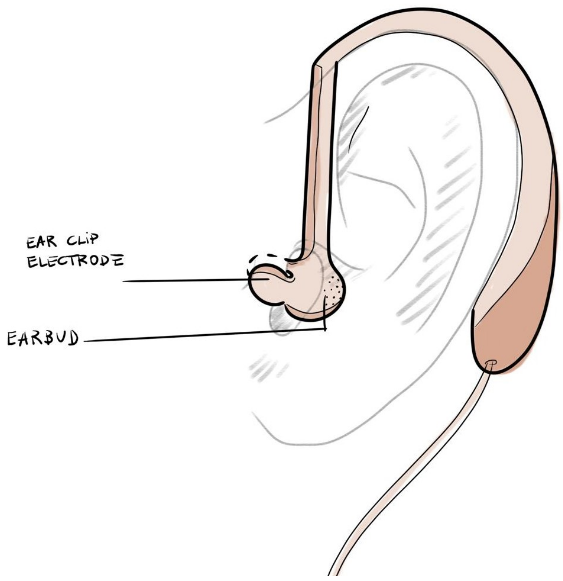


Figure 3.2: Multi-modal stimulation: proposed design for the "auxiliary" component for tragus stimulation

3.4. Stimulation therapies

The device allows for two different ways of stimulation, which differ on the stimulation pattern both of the acoustic and electrical signals.

The first and already existing one is the coupling of *tinnitus-matched tones* with *burst stimulation* (that will be called T1). Burst stimulation has been invented to try to replicate the burst firing of the neurons in the CNS, a phenomenon in which multiple action potentials occur repeatedly in a brief sequence, followed by a long resting period. There are different types of burst stimulation therapy. However, the one that is applied by the device is characterized by sequences (each sequence is a burst) of short electrical pulses (called spikes) with the same amplitude and polarity followed by a charge-balancing period (with a reversed polarity). The polarity reversal that follows each burst presents a scientific explanation behind it: in the burst firing experimented in the nervous cells the spikes correspond to the sodium influx and potassium efflux; the 5 spikes are followed by an "active phase" where a calcium efflux happens from the cell and brings to a decrease in the membrane potential for a certain period.

This technique has already been experimented for VNS paired with tones having frequencies other than the tinnitus one and it has not demonstrated to be superior to simple VNS. However, in this case, the sound frequencies are the same ones that characterize the tinnitus. As already explained above, this therapy should lead to tinnitus habituation [24], [27], [30].

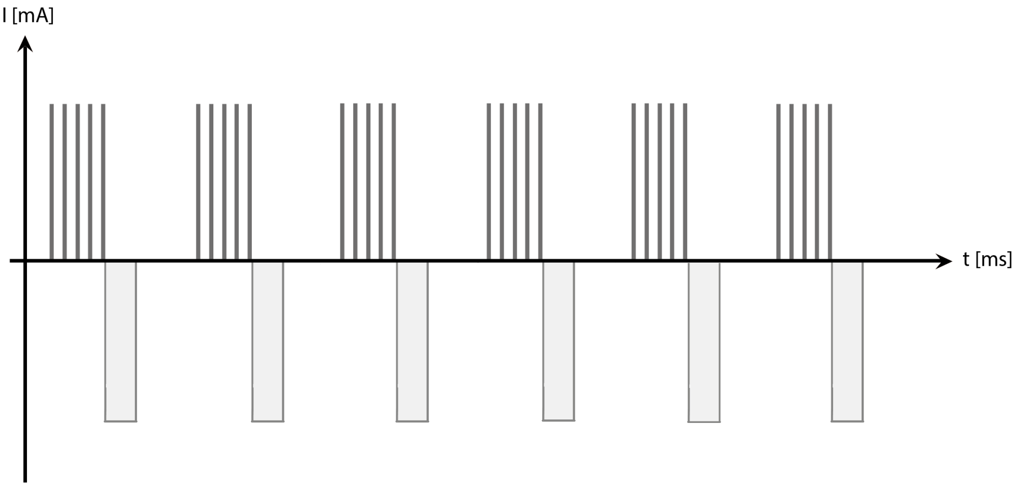
The second type of stimulation is a completely different approach, both in terms of stimulation frequency and pattern. *Tinnitus-matched sounds* are paired with an electrical stimulation consisting in a *"noise + DC" signal* (T2), characterized by a DC component and "spectrally-controlled" noise superposed on it. The noise contains a spectrum in which low-frequencies are amplified and frequencies over a certain threshold strongly attenuated. The DC component switches its polarity after a certain period of time. Due to its unpredictability, this noise stimulation should increase brain salience for lower frequencies preventing habituation [24], [27].

As already mentioned before, depending on if the tinnitus is perceived unilaterally or bilaterally, the device should allow for unilateral or bilateral electrical stimulation. Moreover, it should include an option to apply only acoustic stimulation.

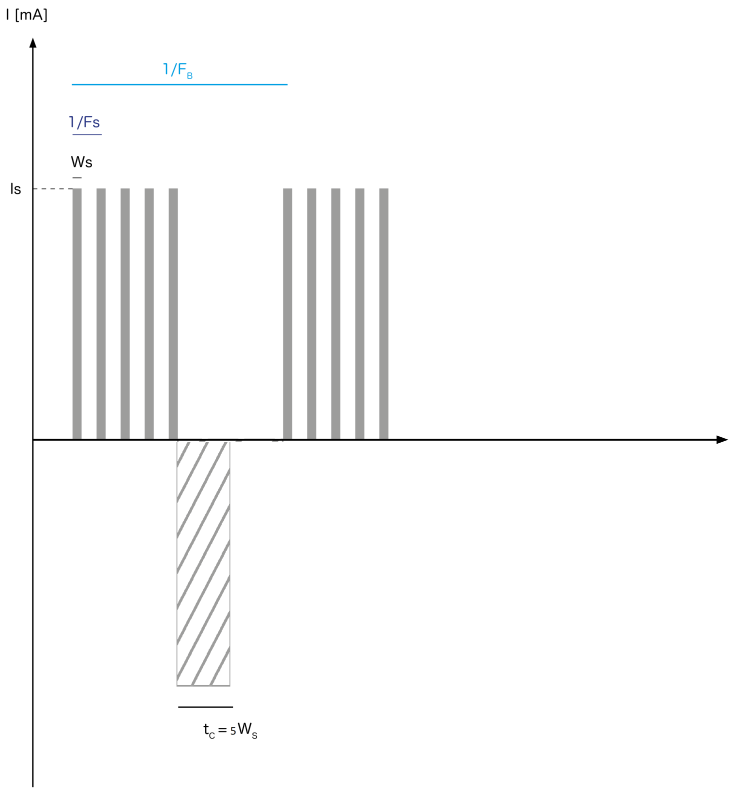
3.4.1. Parameters for multi-modal burst stimulation (T1)

The parameters regarding the electrical burst stimulation (waveform visible in Fig. 3.3a and 3.3b) are the following one:

- Stimulation pattern: current-controlled stimulation, with 5 monophasic spikes per burst followed by a charge-balancing interval (t_C, which is as long as the total width of the spikes: t_C = 5 W_S);
- Stimulation current (I_S): the device should allow to deliver up to 2 mA, with a step size of 0.1 mA;
- Stimulation frequency: there are two different frequencies that must be considered in burst stimulation. The spike frequency (F_S) can be selected between the values in the range 50-500 Hz, while the burst frequency (F_B) in the range 1-50 Hz;



(a) Burst stimulation: multiple bursts with active charge-balancing



(b) Burst stimulation: single burst with active charge-balancing

Figure 3.3: Burst stimulation present in T1

- Pulse width (W_S): it corresponds to the duration of each spike, that can be within 1 and 10 ms (step size: 0.1 ms). The interspike intervals should be of the same duration.

On the other hand, the parameters for the acoustic stimulation of T1 are:

- Sound intensity: the sound produced should be in the range 0-90 dB (90 dB represents the threshold of annoyance for people with normal hearing). The upper threshold may be higher for people with hearing loss;

- Sound frequency: the frequencies of the pure tones should be matched to the tinnitus pitch; therefore, the highest sound frequency should be at least 8 kHz (which is the average upper limit in tinnitus sufferers) [86];

- Sound duration: each tone should last for at least 1 second, meaning that each tone corresponds to at least 1 burst.

In the user interface, there must be the possibility to adjust the following settings: current amplitude, pulse width, spike frequency (which depends on the patient's audiogram), burst frequency, and sound level. The sound frequency range depends on the patient's audiogram and must be kept constant.

3.4.2. Parameters for multi-modal "noise + DC" stimulation (T2)

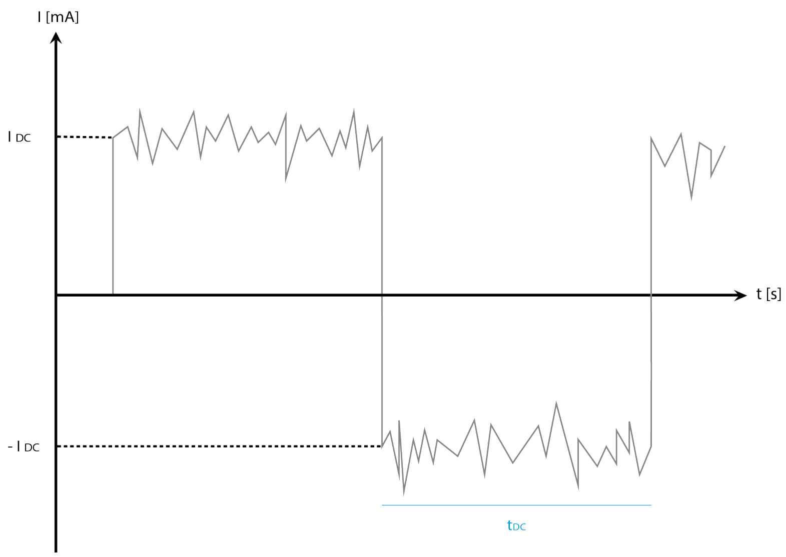


Figure 3.4: Noisy pseudo DC waveform present in T2

The parameters for the "noisy pseudo-DC" stimulation (Fig. 3.4) are:

- Stimulation pattern: current-controlled, biphasic stimulation, with a constant adjustable current and a low- frequency noise component;

- Stimulation current (I_{DC}): it should be programmable between 0.1 and 2 mA, with a step size of 0.1 mA;

- Stimulation frequency: the noise frequency spectrum covers frequencies in the interval 0.01-100 Hz;

- Phase duration (t_{DC}): the duration before each change in DC polarity is within 10 and 100 seconds, with a step size of 1 second;

The acoustic stimulation should be exactly the same one as in T1. Therefore, the multi-modal stimulator should guarantee the playback of at least an 8 kHz tone.
In this case, the user may have only few settings to be inserted for the therapy, which are the level of the direct current, the phase duration, and the sound level.

3.4.3. Combined mode (T3)

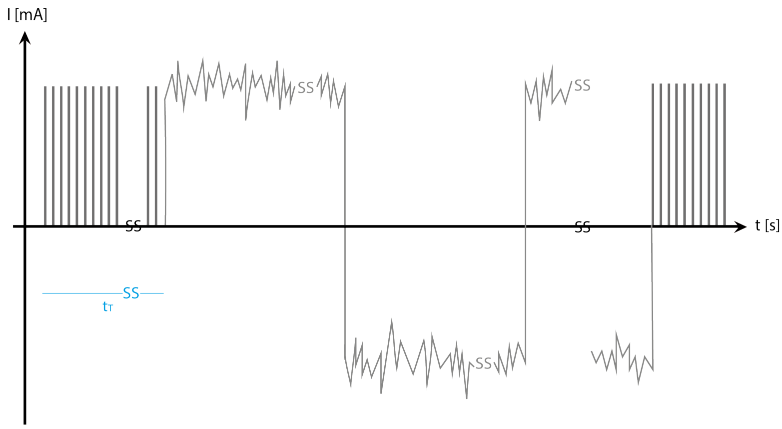


Figure 3.5: Combined therapy present in T3 (each pulse is equal to one burst)

The stimulator gives also the user the possibility to combine the two therapies without the need to stop the stimulation whenever a different stimulation pattern is required. Burst and "noise DC" stimulation alternate during T3 after a preset period of time t_T. For instance, after having selected the parameters for each stimulation and t_T = 30 mins, every 30 minutes the stimulator switches from T1 to T2 and from T2 to T1 (as shown in Fig. 3.5).

3.5. Stimulation duration

There is not a precise requirement regarding the time during which the stimulation should be "ON", but indicatively the device should be used every day for several hours (e.g. 2 hours/day).
The multi-modal stimulator must not be in continuous operation, meaning that each stimulation session may last for minutes as soon as the prefixed hours of stimulation per day are reached at the end of the day.
Moreover, the stimulation must be intermittent, at least for acoustic stimulation: each tone should have a duration of few seconds, followed by an equal period in which the stimulation is interrupted.

3.6. Power source

Since one of the requirements is that the device should be portable (to allow the patient to perform the daily activities without being hindered by the treatment), the best choice is to make it battery-powered.
The battery, either rechargeable or not, should have a capacity high enough to ensure at least a day of stimu-

lation. Rechargeable may be a better option because it would avoid to constantly replace the battery.

3.7. Compliance voltage

Since there is no indication on the size and material of the electrodes that must be used for stimulation, the device must ensure a high voltage compliance. Considering applications used for stimulating the regions of the ears described above (which should be the ones requiring the smallest electrode contacts, and therefore the highest electrode impedance), the voltage compliance should be around V_{CMP} = 20 V, which means that, in the worst case scenario when I_{STIM} = 2 mA, the load should not assume an impedance higher than about 10 kΩ [1].

3.8. Other requirements

Other requirements that must be taken into account are the number of channels, the user interface, the dimensions and weight of the device, and finally the safety.
Firstly, the device should have a *number of channels* sufficient to provide both bilateral acoustic stimulation and electrical stimulation. For performing bilateral acoustic stimulation, just 1 audio channel is required in order to plug the headphones. Important is also to consider the fact that both ears should receive the same audio signal for an identical bilateral stimulation. For the electrical stimulation instead, 1 channel is necessary to stimulate unilaterally (therefore, to drive one electrode pair) , meaning that 2 channels must be present to provide bilateral stimulation. In total, the device must contain at least 3 channels.
The main consideration about the *user interface* is the user-friendliness. Indeed, both doctors and patients must be able to turn on and off the device, and to select the right therapy and the stimulation parameters without particular specific skills and notions. Furthermore, it is not important that the user interface is implemented directly into the device or an external device as long as the portability of the device is guaranteed. For instance, a sufficient solution is to control the device via a simple computer software; however, once the device is configured, it has to be possible to disconnect it from the computer and run the stimulation, otherwise the device is not portable. In this particular case, a small interface must be present in the device itself to control the some important parameters. Indeed, unlike the other parameters, the stimulation current amplitude and sound volume may be easily adjusted during the therapy according to the sensation of the patient.
The user interface must allow to choose:

- Therapy (T1, T2, or T3);
- Parameters of the specific therapy;
- Stimulation duration;
- Monolateral/bilateral electrical stimulation (and so, number of channels active) or acoustic only stimulation.

Finally, the status of the device must be clearly visible. The patients must indeed be aware if the power is almost empty, if the stimulation is activated, and if the device is connected to an external device (e.g. to the computer for the user interface).

The user interface and technology of the device could be improved in a further step only when its functionality and potentiality have been tested. Ideally, the user interface should be included in an application for smartphone, in order to easily control the device at any time.

Linked to the portability of the device are also the requirements for the *dimensions* and *weight*. It should be possible to insert the device into the pocket of a pair of trousers or at least to hook it on top of them. Therefore, the device dimensions must be smaller than 140 x 220 x 50 mm (the dimensions of the pocket for women's trousers) [33]. To allow the patient to move freely, the weight of the device should not be too distant from the one of a normal smartphone, which is maximum 226 grams [123].

Eventually, in terms of *safety* aspects, the device must be able to maintain its proper functionality for temperatures approximately between 0 °C and 40 °C (to be used also in an external environment). Moreover, the stimulation current should not reach levels higher than the threshold of 2 mA, at least not for a prolonged time. A limitation must be inserted for the sound intensity of the acoustic stimulation: the level should not overcome 90 decibels in order not to cause hearing damages [41]. Of course, this limitation may not apply for users who already suffer from a certain degree of hearing loss, which is a great number of tinnitus sufferers.

Finally, if the device is developed in the future in such a way that it communicates wirelessly with a smartphone, safety measures must be included in order to prevent hacking.

Device specifications	
Device function	Portable TENS device and audio player
Stimulation site	Outer ear, mastoid process
Stimulation therapy	Pure tones - Burst stimulation (T1), Pure tones - "Noise + DC" stimulation (T2), combined mode (T3)
Stimulation pattern	T1: current-controlled, 5 monophasic spikes per burst followed by charge-balancing; T2: current-controlled, biphasic, with direct current and selected noise component on it
Stimulation current	max 2 mA (resolution: 0.1 mA)
Pulse width	T1: 1-10 ms ; T2: 10-100 s
Stimulation frequency	T1: Spike frequency: 50-500 Hz, burst frequency: 1-50 Hz; T2: noise spectrum: 0.01-100 Hz
Sound intensity	0-90 dB (for normal people)
Sound frequency	up to at least 8 kHz
Stimulation duration	several hours/day
Power source	Battery (rechargeable or non-rechargeable)
Compliance voltage	20 V
Number of channels	3 (1 for audio, 2 for bilateral electrical stimulation)
User interface	User-friendly
Dimensions and weight	max 140 x 220 x 50 mm, max 226 g

Table 3.1: Summary of the device specifications

4

General architecture and system block diagram

In this section the system design of the mult-modal stimulator is proposed, with a brief explanation of the role of each block. The implementation of each block is instead presented in the next chapter.
The following steps describe the functioning of the multi-modal stimulator:

1. The user sets the stimulation parameters and runs the stimulation;

2. A microcontroller (MCU)reads the instructions given by the user for the creation of the stimulus waveform;

3. An external memory storage contains the pre-processed audio file used for acoustic stimulation. The information encoded in the audio file are then "sent" to the MCU which then conveys them to the audio circuit and finally to the earphones;

4. At the same time, the MCU generates an electrical signal that passes through a stimulation circuit that converts it to a proper electrical current used for stimulation (according to the parameters given by the user).

As it is visible in the diagram in Fig. 4.1, the main component of the stimulator is the *microcontroller*. The microcontroller is able to perform the two tasks required for the functioning of the stimulator: generation of a programmable output electrical signal and communication with external devices.
In particular, it is essential the data exchange between the MCU and the *external memory storage* and with a device used as a *user interface*. The external memory storage is necessary because the microcontroller (at the least the MCUs taken into consideration for this project) does not have a big enough non-volatile memory to

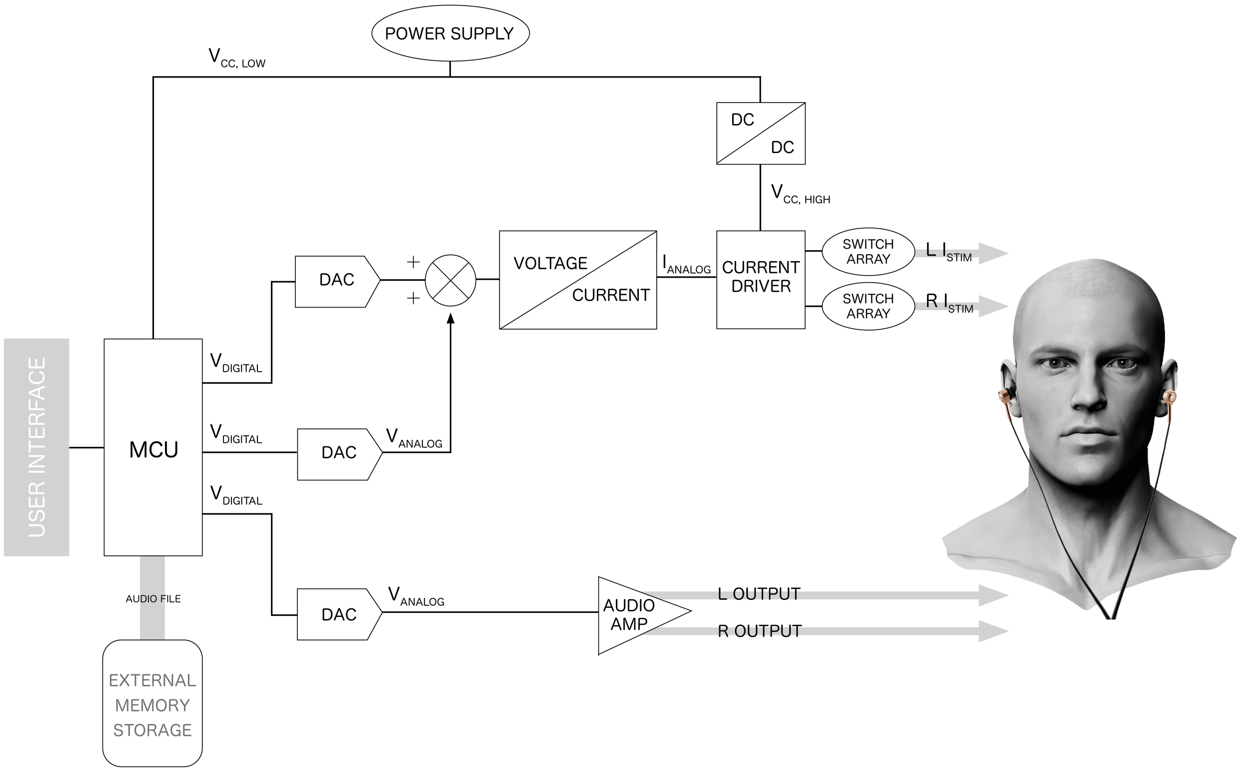


Figure 4.1: Block diagram of the multi-modal stimulator

store audio files. An essential requirement of the microcontroller is its multitasking. The multi-modal stimulator must allow for synchronous acoustic and electrical stimulation, meaning that the microcontroller has to be able to generate both acoustic and electrical stimulation signals concurrently.

Once the correct outputs are generated by the microcontroller, the output signals pass through separate circuits that have the purpose to convert them into the required electrical current and sound. For practical purposes, the circuit that conveys the signal to the electrodes is called the *current generator*, while the one that is converted into sound is called the *sound generator*.

Both the current and sound generator receive a signal from the microcontroller as a sequence of discrete voltages. As a consequence, the first block in both circuits must convert the incoming digital signal into an analog one through a *digital-to-analog converter (DAC)*.

A DAC is present in the architecture of every music player because a sound cannot be obtained from a simple digital signal. Important in audio applications are the resolution and the maximum sampling frequency of the DAC; the resolution represents the number of values that the output signal may assume, while the maximum sampling frequency is the maximum speed at which the DAC can operate and still produce a reliable output. Resolution and sampling rate of the DAC must be chosen depending on the characteristics of the audio file that must be read. At the same time, in the current generator the DAC is essential because it allows the generation of current amplitude of different levels. From this perspective the resolution determines which is the smallest value of current that can be produced. The proper selection of the DAC parameters will be explained in the next chapter. In the section "Circuit for "Noise + DC" stimulation" of the next chapter it will be explained also why two DACs in the current generator are present in the system block diagram.

Moreover, the sound generator could contain either a single or a dual DAC, depending on the number of channels required by the audio file. A stereophonic audio file needs two audio channels because it encodes two different audio signals, while a monophonic audio file requires just a single audio channel to be played. In the system block diagram only one audio DAC is present because the audio file which will be used for stimulation is mono. This choice is due to the fact that a person suffering from bilateral tinnitus must receive the same acoustic stimulation in both the ears. A stereo sound would result in two different sounds being perceived by the ears, which could cause two different stimulation effects.

From this point onwards, current and sound generator are described separately.

Once an analog signal is obtained, the sound generator contains an *audio power amplifier*. The audio power amplifier is used to amplify the power coming from the microcontroller up to a level that ensures that the sound intensity is high enough to be heard via earphones but low enough not to cause hearing damage. Furthermore, an audio power amplifier is needed to drive low impedances characterizing earphones (or speakers). After amplification, the output signal has enough power to be converted into an audible sound by the speaker contained in each earphone.

On the other side, an important matter occurs in the current generator because the analog signal produced by the DAC is still in form of a voltage, while the stimulator requires the control of the output current. Hence, the aim of the next block is to convert the voltage into a current. As the next chapter will explain, there are several ways to realize a *voltage-to-current converter* depending on the requirements of the application (e.g. accuracy, design complexity, space consumption, etc).

The voltage-to-current converter requires to be coupled with a *current driver* circuit. The current driver is used to maintain the value of the current constant regardless of the load impedance. In this application, the load impedance is represented by a model which takes into account both the electrode and the tissue impedance. Unless a stimulator is built to drive a specific electrode, the electrode impedance may not be predicted in advance and it varies depending on the electrode size, geometry, material, etc. Moreover, even when the electrode impedance would be known in advance, the total load of the stimulator can vary significantly, even over time, due to the variation in tissue impedance. The current driver ensures that the current delivered (and thereby the charge) remains always the same. Of course there is a limit to the impedance beyond which the driver is not able to work properly anymore. This limit is determined by the voltage that supplies the driver, i.e. the compliance voltage. The higher the compliance voltage the wider is the impedance range (in terms of modulus) covered by the driver.

Unless a bulky power supply is used, the most straightforward way to obtain an high compliance voltage is to add a *DC-to-DC converter* between the power supply of the multi-modal stimulator and the current driver. A DC-to-DC converter alters the voltage level (either increasing or decreasing) of a source of direct current. In this application, the DC-to-DC converter used is a step-up converter because the output voltage is higher than the input one. The advantage of this choice over other design solutions will be treated in the section treating the device power management. As a consequence, the step up converter allows the the maximum impedance sustained by the driver to be high enough to use a wide variety of electrodes and to stimulate different parts of the body, according to what is required by the device specifications.

The current driver is also the key component for the realization of a bilateral electrical stimulation because two identical output currents will come out from this circuit.

Before the current is fed to the electrodes, a combination of *switches* is used to realize a proper charge cancellation strategy so that the accumulation of charge over the electrode-tissue interface is avoided. Obviously, the same switch pattern is present twice to modify equally the waveform of both the output currents.

Finally, the multi-modal stimulation is provided with a *battery* system as power supply on the basis of its portable nature. Its selection will depend on the operating voltage required by the microcontroller and on other requirements such as form factor.

5

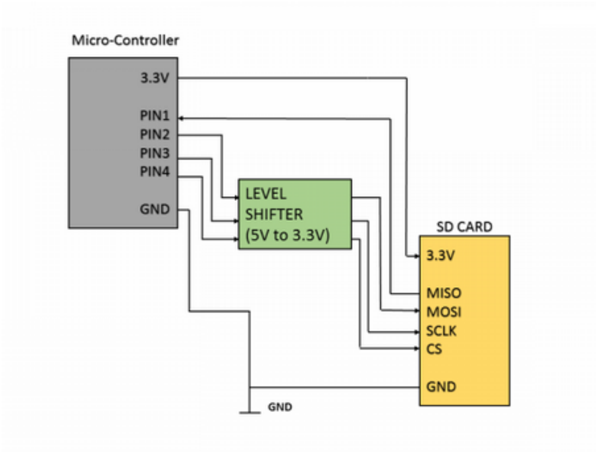
Device design: hardware

5.1. External memory storage and communication protocol

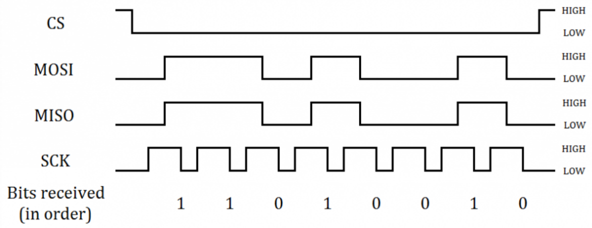
The multi-modal stimulator uses the external memory storage just as a container for a few audio files. Due to the low memory requirements and the relatively small dimensions imposed by the application, a *micro SD card* is used to implement the external memory storage. The micro SD card is the most used form of external non-volatile memory used for portable applications. It is able to guarantee a capacity up to several GB, guaranteeing the storage of audio files of enormous duration. Considering that both the therapies of the multi-modal stimulator involve the same acoustic stimulation, only one audio file is needed to be stored. If the worst case scenario is taken into account, i.e. the audio file is in the WAV format, stereo, with CD quality recording (44.1 kHz sampling rate, 16 bit resolution), the total memory consumption is about 10 MB per minute. As a consequence, the micro SD card would allow to store an audio file of several hours of duration.
The micro SD card communicates with the microcontroller (and any master device) using the SPI protocol. The operation condition register (OCR) present in its digital electronics contains the operating voltage of the device, which is in the range 2.7 V and 3.6 V. Microcontrollers that operate from a larger supply such as the Arduino Uno (5 V) would need a special micro SD card module which provides a voltage regulator to step down the voltage in order not to damage it.
The micro SD card module contains a microcontroller used for communication with the master device that the slave device is ready to start the exchange of data. Six communication lines are required for proper data transfer in SPI mode:
- Master In Serial Out (MISO): it is the line where the data are sent away from the SD card and received by the microcontroller;
- Master Out Serial In (MOSI): transfers the information from the microcontroller to the micro SD card;

- Serial Clock (SCK): sends a digital signal that tells the microcontroller exactly when the bits have to be sampled from the data line (e.g. whenever the clock signal becomes high or low);
- Chip Select (CS): it is the line used by the microcontroller to tell the SD card that has been selected to start a communication with it;
- Power line;
- Ground.

It is important to understand the SPI communication because the presence of the CS, MOSI, MISO, and SCK pins in the microcontroller selected is fundamental for its audio file reading process. It is also important to have it clearly in mind during the phase of microcontroller programming.



(a) Communication buses between microcontroller and SD card [98]



(b) Example of SPI communication protocol [18]

Figure 5.1: SPI communication between an SD card and a microcontroller

5.2. Electrical stimulation circuit

5.2.1. Digital-to-analog converter

As already explained, the first block of the current generator is the digital-to-analog converter. It is essential in both types of electrical stimulation provided by the multi-modal stimulator because it permits the control of the signal amplitude. The chapter regarding the device specifications mentions the fact that the amplitude of the current must be adjustable across an interval of 21 values, from a minimum of 0 mA (i.e. when stimulation is not occurring) to a maximum of 2 mA with a resolution of 0.1 mA. Hence, the application requires at least a 5 bit DAC where the number of bits N is determined by the following equation:

$$N = \log_2\left(\frac{I_{MAX}}{\Delta I} + 1\right) = \log_2\left(\frac{2}{0.1}\frac{mA}{mA} + 1\right) \approx 5 \tag{5.1}$$

where I_{MAX} is the maximum value and ΔI is the resolution (a unit is added in the equation to include the value 0 mA).

Another important characteristics of the DAC is the reference voltage, which is used to define another essential parameter of the DAC for this application, i.e. the dynamic range. The dynamic range defines the difference between maximum and minimum output voltage that the DAC can output. In particular, the maximum output value V_{MAX} is:

$$V_{MAX} = \frac{D_{MAX}}{2^N} \cdot V_{REF} \tag{5.2}$$

where D_{MAX} is the maximum digital input, i.e. 2^N - 1, and V_{REF} is the reference voltage. The reference voltage must be at least as high as the maximum output voltage. Coming back to the device specifications, the maximum output of the current generator is 2 mA. As it will be seen in the next sections, the analog circuit of the current generator is realized in such a way that an output voltage of 2 V from the MCU is converted into a current of 2 mA. This means that the DAC must ensure an output voltage of at least 2 V. This is possible only if the reference voltage is at least 2 V. However, this is not a particular concern for the design used. Indeed, either the voltage supply or an output voltage from the MCU can be used as reference voltage. Most of the microcontrollers work at 3.3 V or 5 V. As a consequence, the minimum reference voltage that can be obtained is 3.3 V, that is in any case sufficient to produce the required maximum output voltage.

The sampling frequency is also extremely important for a correct digital-to-analog conversion in the generation of a noisy stimulus, but this will be discussed in the section regarding the circuit used for noise generation.

Especially significant for burst stimulation is the settling time of the DAC. The settling time represents the time required by the output of the DAC to reach its desired value. In burst stimulation the transition between the low value and the high value must be smaller than the minimum pulse width that each spike may assume, which is 1 ms. If the settling time is longer, the output does not have enough time to reach its specified amplitude.

At this point, the three solutions examined for the implementation of the DAC will be discussed.

The first design approach that may come to mind is the use of an *integrated circuit DAC*. IC DACs are fabricated both in bipolar and CMOS technology and are characterized by several architectures. The most simple one is known as Kelvin Divider or String DAC. If the resolution of the DAC is N, a String DAC is composed of 2^N resistors of the same value in series. Each resistor is separated from the output of the DAC via a switch. The desired analog output is obtained by closing only the appropriate switch of the chain through the digital input word of length N which is translated by a decoder block in the IC. For instance, the string DAC in Fig. 5.2 is a 3-bit DAC with 8 resistors present in series. If Switch k is closed, with simple Kirchhoff equations, the output voltage of the DAC V_{OUT} is:

$$V_{REF} = 8 \cdot RI \tag{5.3}$$

$$V_{OUT} = \frac{kR}{8R} \cdot V_{REF} = \frac{k}{8} \cdot V_{REF} \tag{5.4}$$

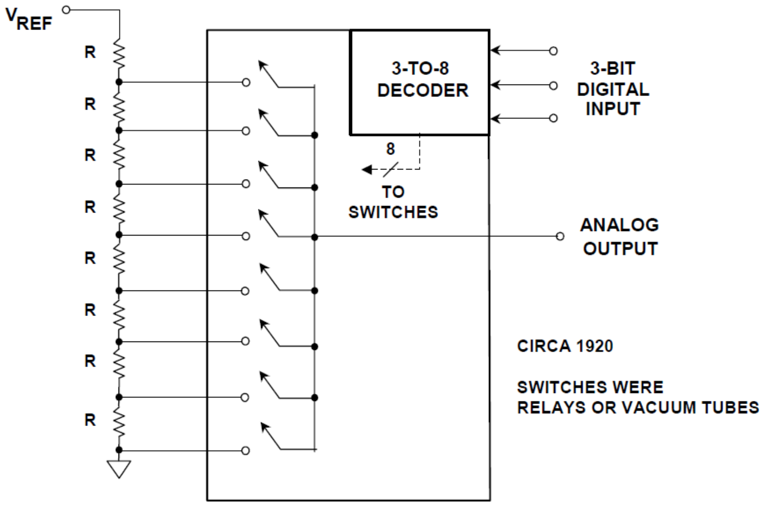


Figure 5.2: Architecture of a String DAC [68]

The multi-modal stimulator requires at least a 5-bit DAC, meaning that the String DAC would be composed of 32 resistors and 32 switches. More complex structures such as the Segmented DACs exist to reduce the numbers of resistors. Moreover, DACs generally include an internal buffer which removes the issue of the high output impedance of the String DAC [68].

In the market there is a massive number of IC DACs that can be selected according to the requirements of the application. An IC DAC may have a resolution that ranges from around 4 to 24 bits (and even higher) and a settling time which can be as low as 1 ns. Moreover, IC DACs may be powered from any single supply voltage. Nevertheless, an IC DAC can consume a significant amount of power as well as space. In particular, considering that two DACs are required for the design of the current generator and that each DAC has to deal with a completely different output (indeed, as it will be explained, one DAC is used to generate noise), the solution of using a dual DAC is not feasible and therefore two separate IC DACs would be needed. Finally, considering that the communication between an IC DAC and a microcontroller is generally SPI-based or I2C-based, the numbers of connections and pins necessary would be quite high considering that two DACs are used, especially taking into account that there is already the micro SD card that must be interfaced to the microcontroller.

The second alternative implementation is the *digital potentiometer*. The digital potentiometer is a mixed signal device born as the electronic version of the mechanical potentiometer with some important advantages: cancellation of space inefficiency, mechanical wearout, wiper contamination, resistance variation, dependency to vibration, temperature, etc. A potentiometer is a three-terminal device with a variable terminal called wiper, which represents the output of the potentiometer. As is visible in Fig. 5.3a, it acts essentially as a voltage divider where the resistive element (in this case R1 and R2) varies according to the input given. The output voltage V_{OUT} is the difference between potentials of the wiper and the negative terminal and is:

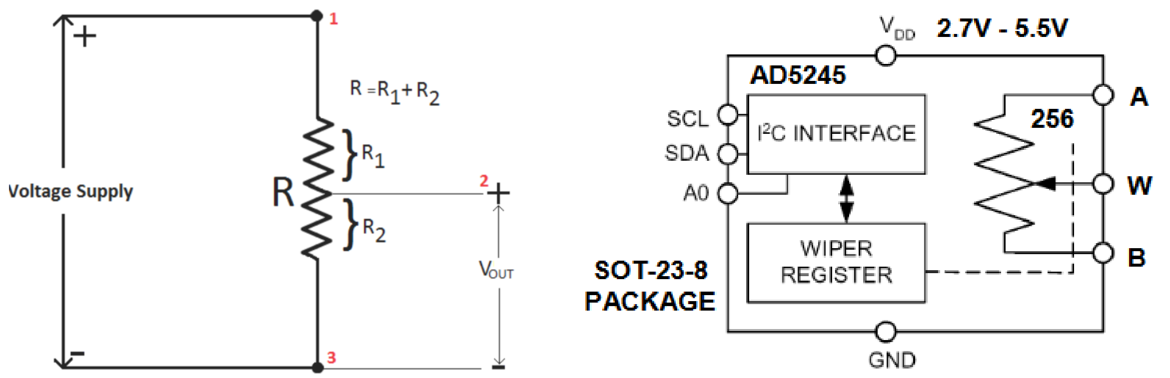
$$V_{OUT} = \frac{R2}{R1 + R2} \cdot V \tag{5.5}$$

where V is the voltage across the resistive element (supply voltage in the figure).

Unlike the mechanical potentiometer where the resistance is varied mechanically by rotating the wiper and modifying the length of the resistive path, in a digital potentiometer the wiper is connected to various points along the resistive element and its position can be controlled digitally via a serial or parallel interface. In this configuration the potentiometer performs as a simple String DAC with the only difference that the negative terminal (terminal B in the figure) is not necessarily connected to ground. The end-to-end resistance R of Fig. 5.3a is the sum of 2^N resistors, where N is the resolution, and it may assume values from 10 kΩ to 1 MΩ. As in the String DAC the output voltage depends on the switch that is closed. If for example the digital input contains the value k, the switch number k is closed and the output voltage V_{OUT} will be:

$$V_{OUT} = \frac{R2}{R_{end}} \cdot V_{AB} \tag{5.6}$$

where R_{end} is the end-to-end resistance and R2 = $\frac{k}{2^N} \cdot R_{end}$ is the resistance across the output voltage.



(a) Potentiometer represented by a variable resistance voltage divider [116]

(b) Internal architecture of the digital potentiometer chip AD5245 [32]

Figure 5.3: Principles of a digital potentiometer

Unlike a normal DAC whose IC is normally composed of sophisticated electronics used to improve its performances, a digital potentiometer chip only contains the digital interface, a wiper register, resistors, and switches, which contribute to an overall power comsumption which is lower than the normal DAC IC. However, the use of a digital potentiometer also presents disadvantages that cannot be neglected for this application.

Firstly, as the simple String DAC it is not able to drive low-impedance loads without an external buffer and its insertion increases both the power consumption and the form factor.

Secondly, the digital interface involves the use of at least two connections per DAC with the microcontroller

and the communication protocol has to be supported by it [68] [32].
To overcome the above mentioned disadvantages, the last option that has been taken into account to convert a digital code into an analog signal is the *PWM DAC*.

5.2.2. Pulse Width Modulation and PWM DAC

Pulse Width Modulation (PWM) is a modulation technique used to simulate the generation of an analog signal from a binary source. A PWM signal is a variable-width rectangular pulse wave which is defined by two components: the duty cycle and the frequency.
The duty cycle is the fraction of the period in which the signal is in an "on" state. Expressed in percentage, it is calculated as $D = \frac{W_P}{T_{PWM}} \cdot 100\%$, where W_P is the pulse width of the PWM signal and T_{PWM} is its period. The frequency of the PWM signal $F_{PWM} = \frac{1}{T_{PWM}}$ describes how fast the signal completes a cycle.
If a PWM signal varies from an "on" and "off" state with a sufficiently high frequency and is followed by a low-pass filter with the cut-off frequency well below the PWM frequency, the output will appear to behave like a constant voltage analog signal where the value of the voltage V_{OUT} is dependent on the duty cycle in the following manner:

$$V_{OUT} = D \cdot V_{ON} \tag{5.7}$$

where V_{ON} is the voltage assumed by the PWM signal in its "on" state (which in the case of PWM generated via a microcontroller is equal to its operating voltage).
In a microcontroller, PWM is generated by an internal timer. Timers are used by the microcontroller to maintain an operation synchronized with the system clock. There are several ways in which timers manage PWM depending on the microcontroller. In general, timers have to cross a all the values contained in an N bits register representing the possible duty cycles. Whenever the timer crosses the value of the corresponding duty cycle, it turns the PWM signal "on", while whenever it crosses the value 0, the signal assumes the "off" state.
However, even if a PWM signal resembles an analog signal, it must be converted to an effective analog signal in order to adjust the amplitude of the output signal generated by the current generator.

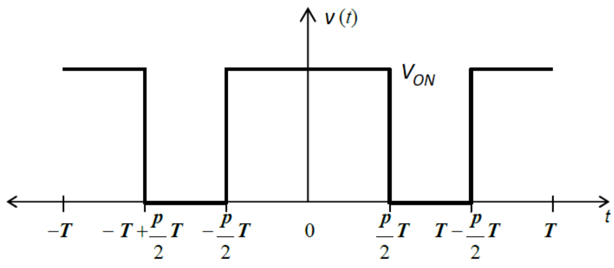
At this point, it is necessary to examine the spectrum of a square wave. An example of a PWM signal with a normalized duty cycle p and a period T is presented in Fig. 5.4a. The signal can be defined as:

$$v(t) = \begin{cases} 0, & -T + \frac{p}{2}T < t < -\frac{p}{2}T \\ V_{ON}, & -T < t < -T + \frac{p}{2}T, -\frac{p}{2}T < t < \frac{p}{2}T, T - \frac{p}{2}T < t < T \\ 0, & \frac{p}{2}T < t < T - \frac{p}{2}T \end{cases} \tag{5.8}$$

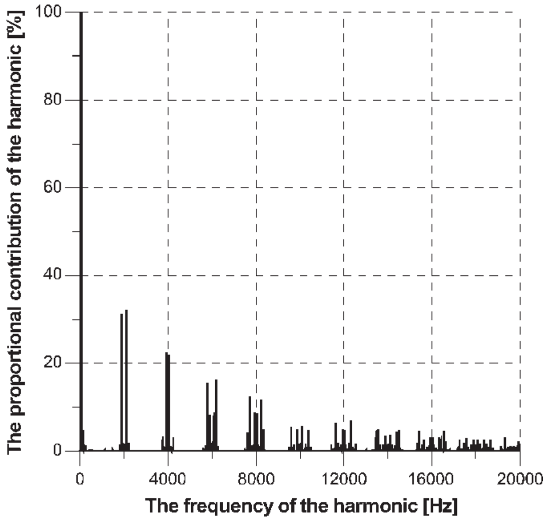
Like any signal, a PWM signal (in terms of voltage) can be written as the sum of infinite harmonics, represented by cosine and sine waves with different amplitudes and harmonics of the PWM carrier frequency, by computing the Fourier series:

$$v(t) = V_0 + \sum_{k=1}^{\infty} V_n \sin\left(\frac{k\pi t}{T}\right) + \sum_{k=1}^{\infty} B_n \cos\left(\frac{k\pi t}{T}\right) \tag{5.9}$$

where V_0 is the amplitude of the DC component and V_n and B_n the amplitude of the other components. V_0 can be written as:



(a) PWM signal with pulse width p and period T shifted at the origin



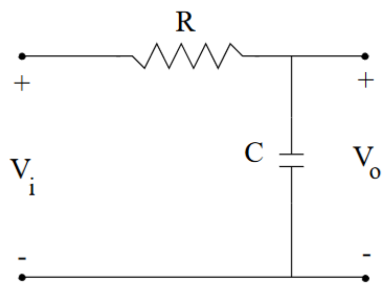
(b) Frequency spectrum of a PWM signal [45]

Figure 5.4: Representation of a Pulse Width Modulated signal

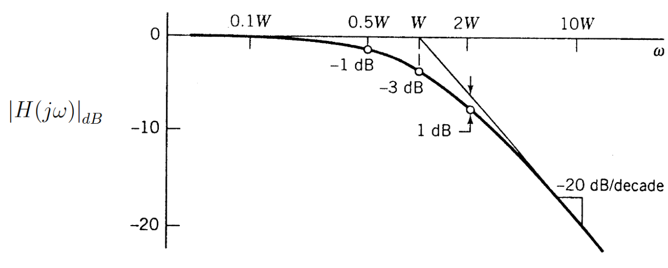
$$V_0 = \frac{1}{2T}\int_{-T}^{T} v(t)dt = \frac{1}{2T}\left(\int_{-T}^{-\frac{p}{2}T} V_{ON}dt + \int_{-\frac{p}{2}T}^{\frac{p}{2}T} V_{ON}dt + \int_{T-\frac{p}{2}T}^{T} V_{ON}dt\right) = p\cdot V_{ON} \tag{5.10}$$

while B_n is equal to 0 and each amplitude V_n (which are described by a complex equation that it will not be discussed) is inversely proportional to the number k of the corresponding harmonic.

From the expression above, it is clear that the elimination of all the frequencies of the PWM signal except for the DC component would result in the generation of a DC signal that can be controlled via the adjustment of the PWM duty cycle. Ideally, this is possible to do, but in practise the harmonics will never be completely suppressed. However, their attenuation is possible via the use of a low pass filter. The combination of a PWM signal and a low pass filter gives birth to a *PWM DAC*.



(a) Schematic representation of a first-order passive low pass filter



(b) Frequency response of a first-order passive low pass filter

Figure 5.5: First-order passive low pass filter [55]

The choice of the low pass filter determines the precision of the output signal of the PWM DAC and so its ripple. The higher the order of the filter the steeper is the roll-off of its transfer function, meaning that the greater will be the attenuation of the unwanted frequencies. Of course, the more complex the filter the higher is the number of components required and so the bigger is the form factor. At that point, an actual DAC would be preferred. However, since the resolution of the output current required by this application is not so high, an high-order low pass filter is not necessary.

A sufficient approach for this application may be the use of a simple *first-order passive low pass filter.* As seen in Fig. 5.5a, the simplest low pass filter is made of a resistor in series with the load and a capacitor in parallel with it. At low frequencies the reactance of the capacitor stops the signal obliging it to pass through the load, while with the increase of the frequency the reactance decreases until the point in which the capacitor acts as a short circuit.

The voltage transfer function of the RC filter is:

$$H(s) = \frac{1}{1+\tau s} \tag{5.11}$$

where τ = RC is the time constant of the filter that defines its cut-off frequency f_C (and therefore its bandwidth):

$$f_C = \frac{1}{2\pi\tau} = \frac{1}{2\pi RC} \tag{5.12}$$

In order to remove most of the harmonics, high values of resistance and capacitance must be chosen. However, it is necessary to keep in mind that the cutt-off frequency is inversely proportional to the rising time of the output signal of the PWM DAC. If a too long rising time is chosen, the waveform of burst stimulation of the output current will be altered when a short pulse width is present.

The rising time is:

$$t_R \approx \frac{0.35}{f_C} \tag{5.13}$$

A good balance is to select the values R = 10 kΩ and C = 22 nF that results in f_C = 723 Hz and $t_R \approx$ 0.4 ms [21]. In the case of a first-order passive low-pass filter, the peak-to-peak amplitude of the output voltage ripple V_{ripple} can be found through the following equation:

$$\frac{V_{ripple}}{V_{ON}} = \frac{T}{4 \cdot RC} \tag{5.14}$$

$$V_{ripple} = \frac{V_{ON}}{4 \cdot F_{PWM} \cdot RC} \tag{5.15}$$

where F_{PWM} is the frequency of the PWM signal [128].

Now, assuming that a microcontroller with a 5 V operating voltage is selected such as the Arduino Uno (which is the case) and that the PWM frequency F_{PWM} is between 100 kHz and 200 kHz (which is possible since the PWM frequency is a multiple of the clock frequency of the microcontroller and the microcontrollers that will be taken to consideration are working at at least several MHz), the voltage ripple will be in the range $V_{ripple} \approx [28; 57]$ mV. Hence, in any case it will be way lower than the limit imposed by the resolution of the output signal (that, as can be deduced by the explanation of the voltage-to-current converter, will be 100 mV).

The advantages of using PWM DAC over a normal DAC or a digital potentiometer are evident for this application.

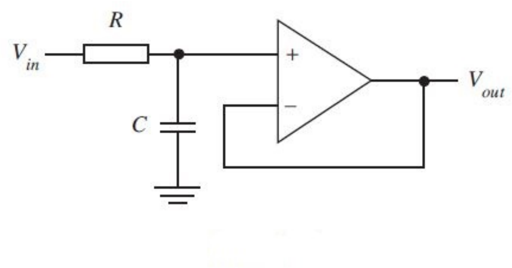
Apart from the output accuracy, which is not a concern since the resolution required for the design of the multi-modal stimulator is not so high, all the other requirements lead to the choice of the PWM DAC.

Firstly, the low pass filter requires just a simple input PWM voltage referenced to ground, which is easily obtainable via the connection of just one PWM pin provided by the microcontroller.
Secondly, a first-order passive low pass filter needs just two components, one resistor and one capacitor. Therefore, it has a clear advantage in terms of space consumption over the other solutions.
Then, in terms of programming, the already existing architecture in the microcontroller and the simple code required to generate a PWM signal eliminates the need of a program to digitally interface with the ICs.
Also the associated costs are lower than those of an IC DAC or a digital potentiometer (but this is not a particular requirement for the multi-modal stimulator).
Regarding the second DAC present in the system block diagram, it will be also implemented via a PWM DAC, but a further explanation on the choice of the components will be included in the section treating the Noise + DC signal generation.
A PWM DAC with a first-order passive low pass filter has however two issues that may be considered: the resolution of the duty cycle and the output impedance.
The resolution of the duty cycle, which corresponds to the resolution of the output voltage of the PWM DAC, is dependent on the number of bits encoding the timer registers of the microcontroller. For instance, the timers present in the Arduino Uno are at least 8-bit timers, meaning that the number of duty cycles allowed for the generation of the PWM output signal is 256. This number is way higher than the total number of duty cycles required to generate a voltage from 100 mV to 2 V (2 V is the output voltage used to obtain a 2 mA output current). In fact, a PWM DAC can output a voltage lower than the operating voltage, which is 3.3 V or 5 V depending on the device. Hence, to reach the minimum step of 100 mV, the duty cycle resolution has to be 6 bits (indeed, the number of duty cycles allowed must be 3.3/0.1 = 33 or 5/0.1 = 50), which does not create any problem.
The second issue related to passive filters is their poor load-driving capability. In case of a passive first-order low pass filter, the output impedance is equal to the parallel connection of the resistance R and the capacitive reactance $Z_c = \frac{1}{jwC}$, meaning that for low frequencies the output impedance tends to R (which is a high value if a resistance of 10 kΩ is used). As a consequence, if the resistance is sufficiently high, the output voltage may be lower than the one desired if the input impedance of the following stage is not high enough. The problem can be solved by inserting a voltage follower after the low pass filter. A unity-gain follower is characterized by a very high input impedance that prevents excessive loading on the filter and at the same time preserves its output signal. Moreover, the high input impedance of the amplifier avoids a dependency of the cut-off frequency. Once the buffer is included, its gain bandwidth may be a cause of signal attenuation. However, the frequencies involved in burst stimulation are low enough to be inside the pass-band of basically every amplifier (BW ≥ 500 Hz). The addition of a buffer per PWM DAC increases both the power and area consumption of the chip, leaving only the advantage of the design simplicity.
In conclusion, the need of a buffer can be avoided if a low resistance of the filter is selected and if the next stage of the stimulator has a sufficiently high impedance (the output impedance of the filter is represented by the input resistors of the summing amplifier, which can be chosen of any value, even very high one). However, there are ICs available that include more than one pamp, such as the LT1079 that has been chosen to implement

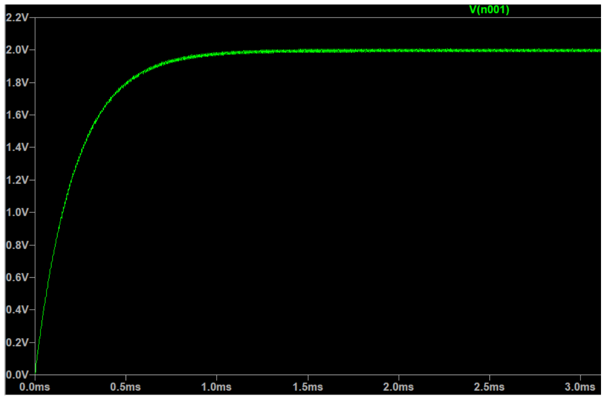
all the three OPAMPs present in the design of the multi-modal stimulator. In this sense, the presence or absence of the buffer does not change the area consumption of the device. For this reason, the final implementation for the digital-to-analog converter is the *first-order passive low pass filter* followed by a *buffer* [5].

The selection of a proper OPAMP is not that difficult. The amplifier must be rail-to-rail because the input coming out the PWM DAC has to be perfectly replicated at the output. Indeed, some amplifiers cannot go below a certain output value (e.g. 300 mV). Secondly, the input range has to be at least from 0 to 2 V, in order to allow the multi-modal stimulator to generate a current output of 2 mA. Then, it has to support a 9 V voltage single supply (coming from the battery). Finally, it must be suitable for battery-powered applications, meaning that the supply current must be low. As last requirement, the OPAMP has to be fast enough so as not to compromise the rectangular shape of each spike present in the burst stimulation (altering significantly the charge delivered to the tissue on each burst, compared to the one of the active charge-balancing period). Hence, a good balance between power consumption and slew rate has to be taken into account in the selection of the OPAMP.

In the end, as already mentioned, the IC that has been chosen is the LT1079, a micropower quad OPAMP that will be used to implement all the amplifiers required by the design of the multi-modal stimulator.



(a) Schematic representation of a buffered first-order passive low pass filter



(b) LT Spice simulation of the transient response of a PWM DAC (R = 10 kΩ, C = 22 nF, F_{PWM} = 150 kHz, duty cycle 20%, PWM from a microcontroller operating at 5 V

Figure 5.6: First-order passive low pass filter followed by a buffer amplifier

	GENERAL DAC	DIGITAL POTENTIOMETER	PWM DAC
Hardware complexity	quite complex (multiple blocks present inside the IC)	quite simple	simple
Software complexity	not simple (interface with the IC required)	not simple (interface with the IC required)	basic
Area consumption	high (including wires for MCU interface)	high (including wires for MCU interface)	variable (very low if no buffer)
Power consumption	variable (depending on resolution, sampling rate, etc)	low	low (most power for PWM switches control)
Resolution	$\leq$ 24 bit	$\leq$ 10 bit	$\geq$ 8 bit (depending on Timer resolution)
Settling time	very fast (up to 1ns)	fast ($\leq 1\ \mu$s)	variable (trade off ripple/settling time)

Table 5.1: Comparison of the different implementations of a digital-to-analog conversion block

5.2.3. Circuit for "Noise + DC" stimulation

Burst stimulation requires just a simple DAC to obtain an analog signal used to adjust the current amplitude. The other parameters of the waveform are regulated through the blocks that are explained afterwards (voltage-to-current converter and switch array).

However, the multi-modal stimulator must be able to provide also a second type of electrical stimulation, which is composed of both a DC component and noise. The noise component is the important issue that must be faced: due to its well defined spectrum and so its non-random behaviour, it cannot be simply programmed in software via a repetition of random duty cycle PWM signals that then are fed to the PWM DAC through the use of a random number generator. The noise is indeed composed of amplified frequencies in the range 0.01-100 Hz.

A solution that may come up in mind is the combination of an analog circuit which acts as a random number generator followed by a low pass filter with a sufficiently large roll-off to attenuate frequencies higher than 100 Hz. The numbers generated by the random number generator must consider the fact that a programmable DC offset must always be present in the signal. This design may be complex in many ways.

However, another solution exists. As already explained, the multi-modal stimulator reads an audio file and then outputs the values encoded in it to generate a sound through the sound generator. Both in case of monolateral and bilateral tinnitus, the perfect acoustic treatment is the one that is based on an equal stimulation of both sides of the auditory system. In this sense, the ears should receive exactly the same sound, meaning that the audio file required is mono. If instead stereo audio files are used, the second channel is going to be free-of-use. This means that a single audio file can be used contemporarily for acoustic and electrical signal generation: one channel can feed the sound generator and one the current generator. In this way, via digital sound processing one of the two signals of the audio file can be programmed as a sequence of pure sinusoidal tones (for acoustic stimulation) and the other one as spectrally-modified noise. The software Audacity that will be described in the chapter "Device design: software" allows to generate a white noise signal and then to digitally filter it in such a way as to satisfy the requirements for this application.

At this point, the stereo audio file can be converted to 8 bit and its values can be treated as duty cycles used for PWM signal generation by the microcontroller. The current generator can use as already explained a PWM DAC to convert the PWM signal into an analog one.

A final issue however must be solved. The noisy signal coming out of the PWM DAC is characterized by an offset which cannot be modified and which is presumably a value around 2.5 V (the audio file is 8 bit, and therefore the values encoded are between 0 and 255, which correspond to an analog value produced by the PWM DAC between 0 and 5 V; hence, the offset of the signal is around the middle value).

As a consequence, an analog circuit must be designed that is capable of removing the predetermined DC offset and of adding an offset of the desired amplitude. The circuit for "noise+ DC" signal generation must be composed of two *PWM DACs* and a *summing amplifier*. One PWM DAC is used to generate an analog constant signal used both for the burst waveform and for the DC offset, the other one for noise signal generation. Moreover, the second DAC must be followed by a *coupling capacitor* to remove the already present offset.

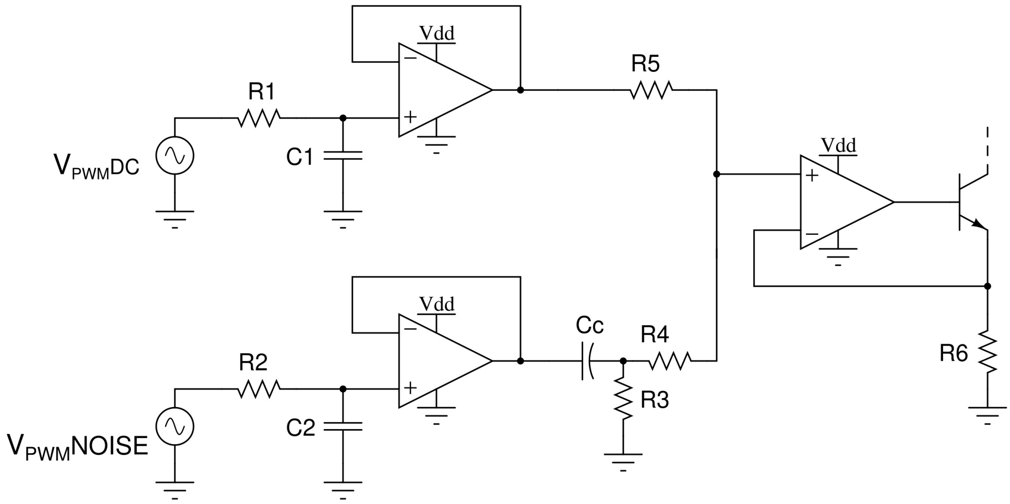


Figure 5.7: Circuit used to realize the "noise+ DC" waveform

The circuit is entirely described by Fig. 5.7.

The selection of the components for the upper PWM DAC has already been described before. The load of the low pass filter depends on a complex relation between R5, R4, R3, and Cc, making it difficult to select the right values in order not to have problem in driving the desired output voltages for the filter. The same issue stands for the second PWM DAC. For this reason, both the PWM DAC are realized with a low-pass filter and a buffer. Both the buffers are implemented with the same IC LT1079.

The requirement in the selection of the values for R2 and C2 is again the cut-off frequency. In the device specifications the noise presents 100 Hz as the highest frequency. As a consequence, the combination of the resistance and capacitance must ensure that the cut-off frequency is higher than that value. A good solution may be R2 = 100 kΩ and C2 = 10 nF ($fc \simeq$ 159 Hz).

Although the low-pass filter is effective in removing unwanted high frequency components, the noise signal coming out of the PWM DAC still presents very low frequency components that are not included in the device specifications: frequencies below 0.01 Hz, including the DC component, have to be removed. This burden is reserved to the coupling capacitor Cc and resistor R3, that together generate a first-order high pass filter, with a cut-off frequency equal to:

$$f_{cut-off} = \frac{1}{2\pi \cdot CcR3} \tag{5.16}$$

The first-order high-pass filter presents the same poor load-driving capability of the first-order low pass filter. As a consequence, the value of R3 has to be significantly lower than those of resistors R4 and R5.

Moreover, the transfer function of the circuit with the only DC input voltage active and output corresponding to the voltage at the positive input of the amplifier on the right of the figure is:

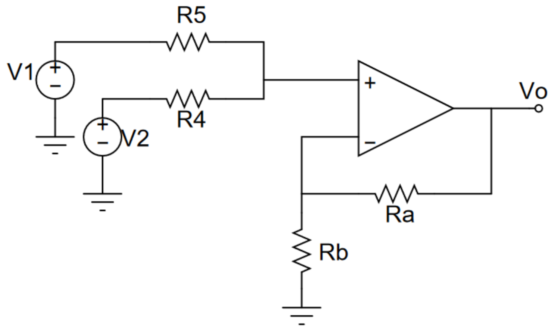
$$H = \frac{R7 + R8}{R7 + R8 + R9} \tag{5.17}$$

The equation imposes a correct selection of the resistors values in order not to introduce an unwanted DC offset. At the same time, too high values for R8 and R9 should be avoided; in this case, the input bias currents at the input of the right amplifier may introduce an offset that could compromise the accuracy of the output.

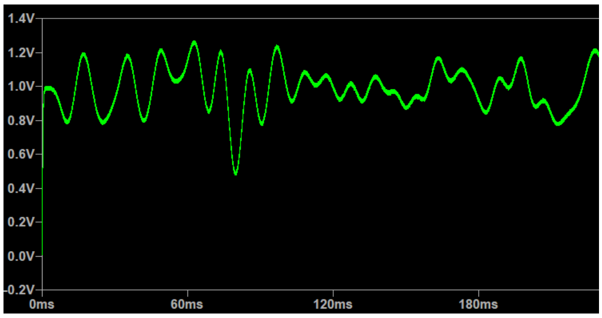
The value of the coupling capacitor must be sufficiently high not to provide attenuation to the noise frequencies. In the end, the values selected are Cc = 1000 μF and R3 = 2 kΩ ($f_{cut-off} \simeq$ 0.07 Hz). Resistors R4 and R5 are instead chosen to be 100 kΩ.

The last block of the circuit is used to sum the two analog signals coming from the PWM DACs. For this purpose a non-inverting summing amplifier is designed, which corresponds to the right part of Fig. 5.7 (excluding the transistor, which together with the OPAMP forms the voltage-to-current converter that will be described below).

The general non-inverting summing amplifier is visible in Fig. 5.8a.



(a) General non-inverting summing amplifier



(b) LTSpice simulation of the "noise + DC" stimulation circuit: the DC input is set to 2 V, while the other source is a reproduction of the noise required by the application and an unwanted offset set to 2 V. The signal shown is the output voltage of the summing amplifier

Figure 5.8: Details of the "noise + DC" stimulation circuit

The transfer function of the circuit is:

$$H(s) = \left(1 + \frac{Ra}{Rb}\right) \cdot \left(V1 \cdot \frac{R4}{R4 + R5} + V2 \cdot \frac{R5}{R4 + R5}\right) \tag{5.18}$$

In order to have the sum of the DC and the noise component, the voltage gain Av = $1 + \frac{Ra}{Rb}$ must be equal to 1. Hence, since the resistor R6 in the final design has a fixed value used for the voltage-to-current conversion, a unity gain is obtained by simply shorting resistor Ra.

Now, the choice of the values for R4 and R5 are dependent on the voltage-to-current conversion explained in the following section. Indeed, the current obtained by the conversion is two times the input voltage (referring to mA and V as units). Therefore, in order to maintain a perfect correspondence between the output voltage of the PWM DAC and the output current, the output voltage of the summing amplifier should be halved (as seen in Fig. 5.8b). This is possible by simply choosing equal values for R4 and R5.

Burst stimulation is not compromised by the configuration. Indeed, if the PWM signal entering the lower PWM DAC has a duty cycle equal to 0, the output is also 0 V. Therefore, only the input from the upper PWM DAC determines the amplitude for burst stimulation.

In conclusion the IC LT1079 is used to implement the OPAMP present in the summing amplifier. In this way the same integrated circuit realizes all the OPAMPs required by the design.

5.2.4. Voltage-to-current converter and current driver

The current generator of the multi-modal stimulator delivers a current, meaning that, once the desired voltage is achieved through the summing amplifier, it has to be converted into a current. The voltage-to-current converter must ensure:

- an output current range of 0-2 mA, with a precision of 0.1 mA;
- an output current that does not depend on the loaf (thereby a high output impedance);
- a voltage headroom low enough not to affect the compliance voltage indicated in the device specification (20 V);

- a fast settling time (that should not influence the burst stimulation waveform);
- bilateral stimulation (i.e. two output currents as similar as possible);
- a limited power consumption;
- a limited number of components.

A current source may be implemented via a specific *integrated circuit.* Analog Devices offers several alternatives, but all of them present an output current range that is not suitable for the application. In particular, the minimum output current that they are capable to handle is 0.5 mA, which is way higher than what expected. The only applicable IC current source is The LM334, which has a programmable output current from 1 to 10 mA, may operate at 20 V, and present a very high output impedance (well over 1 MΩ). The slew rate is also high for the range of currents of this application. The voltage-to-current conversion is dependent on an external sense resistor and on the bias current of the IC. According to the datasheet, the output current would be:

$$I_{OUT} \simeq 1.06 \frac{V_R}{R_{SET}} \tag{5.19}$$

where V_R is the voltage across R_{SET}, the sense resistor. V_R is a fixed value that depends only on the temperature (if the device is working at room temperature the value is around 64 mV). Therefore, it is clear that, in order to control the output current, R_{SET} has to be implemented via a digital potentiometer, which guarantees a minimum resistance of at least 64 Ω and a maximum of at least 680 Ω. Moreover, a potentiometer with a very high resolution must be chosen. Indeed, the smallest resistance resolution required is 1.9 Ω (it is the difference between the resistor value required for 2 mA output current and the one for 1.9 mA). A potentiometer with such a high resolution for a small range of resistances may be very difficult to find or may require further resistive elements, making the design complex.
A second possible approach is the *improved Howland current pump*, visible in Fig. 5.9.

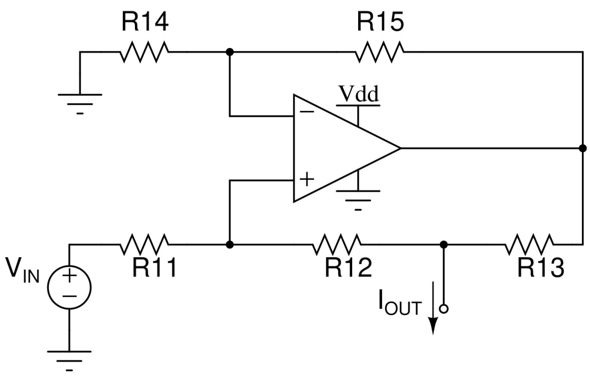


Figure 5.9: The improved Howland current pump

The output current of the circuit is calculated from the following equation:

$$I_{OUT} R_{13} \left[1 + \frac{R_{14}}{R_{15}} + R_L \left(\frac{1}{R_{15}} \cdot \frac{1 - \frac{R_{14}}{R_{15}} \cdot \frac{R_{12}}{R_{11}}}{R_{13}} \right) \right] = V_{IN} \left(\frac{R_{12}}{R_{11}} + \frac{R_{14}}{R_{15}} \cdot \frac{R_{12}}{R_{11}} \right) \tag{5.20}$$

where R_L is the load resistance. If the resistances are selected such that $R_{14} = R_{15} = R_{11} = R_{12}$, the equation is simplified as:

$$I_{OUT}R_{13}\left(2+\frac{R_L}{R_{15}}\right)=2V_{IN} \tag{5.21}$$

Then, if R_{15} is chosen sufficiently high, it becomes:

$$I_{OUT}\simeq\frac{V_{IN}}{R_{13}} \tag{5.22}$$

Hence, the output current becomes directly proportional to the output voltage of the summing amplifier by a factor which is regulated by the value of R_{13}. In order to balance the effect of the summing amplifier over the output voltage of the PWM DACs (the voltage is halved), the resistor value must be selected R_{13} = 500 Ω. In this way, for instance in case of burst stimulation, a 2 V signal coming out of the PWM DAC will be converted into a 2 mA current.

Unfortunately, this configuration presents some limitations. First of all, an accurate conversion is possible only if there is a good matching between all the resistors; therefore, their value must have an accuracy of at least 1%. Variations may alter the above equation, introducing an error in the output current.

Secondly, the voltage drop over R_{13}, together with the possible limitation at the output of the OPAMP, could limit the compliance voltage.

Finally, the Howland current source does not manage to solve the problem of the bilateral stimulation because it allows to control only a single output current. Hence, two Howland current sources would be needed. [62] [61].

The solution that has turned out to be capable of fulfilling all the requirements is a *transconductance amplifier* followed by a *double-output current mirror* (in Fig. 5.10) .

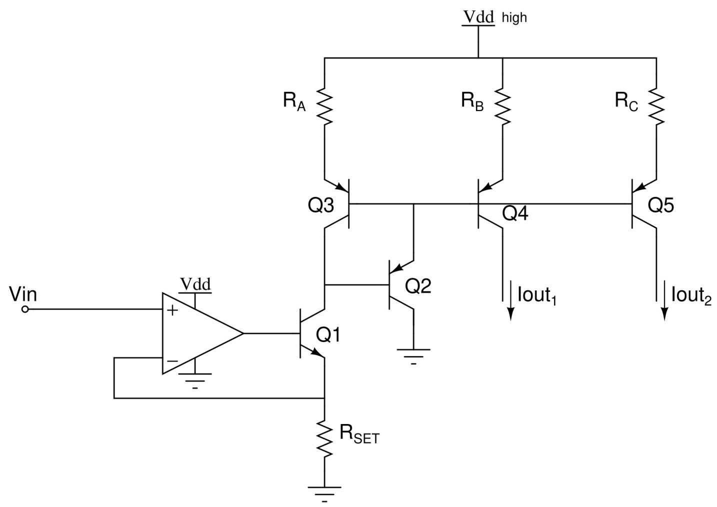


Figure 5.10: The transconductance amplifier combined with an "improved" double-output current mirror based on PNP bipolar transistors

The transconductance amplifier is realized with the combination of an OPAMP, a NPN bipolar transistor Q1 (or equivalently an N-channel MOSFET), and an high precision resistor R_{SET} that determines the transconductance. The base current of the transistor controls the emitter current I_{Q1} and, due to the virtual ground of the OPAMP, its positive input voltage is replicated at the emitter. In this way:

$$I_{Q1} = \frac{V_{in}}{R_{SET}} \tag{5.23}$$

For the same reason, as mentioned in the discussion on the Howland current pump, the value of the resistor has to be R_{SET} = 500 Ω.

The second part of the circuit is a PNP-based current mirror with two outputs. Thanks to this configuration, the current flowing through Q1 works as the input current of the current mirror, which is therefore proportional to the currents of Q4 and Q5 by a factor of N. If Q3, Q4, and Q5 are identical in terms of base-emitter areas, then N ≃ = 1.

Actually, the factor N is not exactly equal to 1, but contains an error that is introduced by the current gain β of the transistors. In the normal configuration of the current mirror (assuming the base-emitter areas are the same):

$$N = \frac{\beta}{\beta+2} \tag{5.24}$$

The dependency on the current gain is reduced by introducing the β *compensation* with the transistor Q2, in which the factor N is equal to:

$$N = \frac{\beta^2+\beta}{\beta^2+\beta+2} \tag{5.25}$$

In this way, if transistors with sufficiently high β are chosen, N becomes almost identical to 1. This means that the output currents of the multi-modal stimulator will be:

$$I_{out1} = I_{out2} = I_{Q1} \tag{5.26}$$

Another improvement to the normal current mirror has been introduced in this design: the *resistive degeneration.* The emitter resistors R_A, R_B, and R_C are used to increase the output impedances of the circuit. Indeed, if they are absent, the output impedances would be:

$$Z_{out1} \simeq r_{CE4} \tag{5.27}$$

and

$$Z_{out2} \simeq r_{CE5} \tag{5.28}$$

where r_{CE4}, and R_{CE5} are the collector-emitter resistances of Q4 and Q5.

But the presence of the emitter resistors increases them to:

$$Z_{out1} \simeq r_{CE4} + R_B + g_{m4} r_{CE4} R_B \tag{5.29}$$

and

$$Z_{out2} \simeq r_{CE5} + R_C + g_{m5} r_{CE5} R_C \tag{5.30}$$

where g_{m4} and g_{m5} are the transconductances of Q4 and Q5 [23].

The trade-off at this point regards the compliance voltage and the output impedance. Indeed, the value of the emitter resistors has to be chosen in such a way that the output impedance is very large and the compliance voltage is not affected too much by the voltage drop over the resistors. The value that has been selected for the emitter resistors is $R_A = R_B = R_C = 330\ \Omega$, meaning that the maximum voltage headroom is $V_{headroom} = R_A I_{outMAX} = 660$ mV (excluding the voltage drop over Q4 and Q5).

The use of the current mirror avoids the need to power the OPAMP with a high voltage, reducing therefore its power dissipated. The settling time for burst stimulation depends again primarily on the slew rate of the OPAMP. However, the summing of DC and noise signals is done passively and the resulting voltage is converted into a current directly, without the need for an extra (voltage) amplifier, reducing therefore the influences on the settling time and also saving space and components. The IC LT1079 permits to implement all the OPAMPs present in the multi-modal stimulator.

In order to reduce as much as possible the transistors' mismatch that would lead to inaccuracies in the two output currents, the 4 PNP transistors are implemented with the quad transistor IC MPQ3799. Transistors with a high β like the one in MPQ3799 eliminate almost entirely the deviation in the current mirror factor N from the desired value 1.

The biggest advantage of this solution is that a bilateral stimulation is possible thanks to the two (almost) identical output currents that the current mirror is able to deliver. Following the other approaches, a bilateral stimulation may only be possible to realize by duplicating the current source and adding further buffers after the summing amplifier. However, the current mirror allows to obtain two outputs with the addition of a simple PNP transistor (Q5).

Moreover, as long as the limitations in the load imposed by the compliance voltage are respected, the output current range is completely satisfied, as well as the precision as visible in the results of the LTSpice simulation shown in Fig. 5.11.

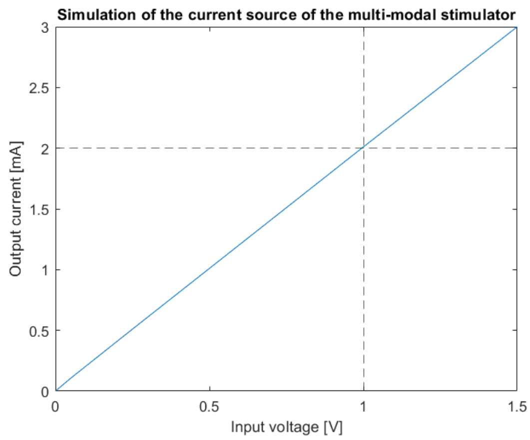


Figure 5.11: Input-output relation of the transconductance amplifier combined with the "improved" double-output current mirror (loads over the two outputs $R_{load1} = R_{load2} = 1\ k\Omega$)

For all the explanation given above, the transconductance amplifier combined with the "improved" double-output current mirror is the final choice for the design of the voltage-to-current converter and current driver of the multi-modal stimulator.

5.2.5. Circuit for bidirectional stimulation

The last block of the current generator is used for two main reasons. First of all, the current delivered to the tissue, especially for "noise + DC" stimulation, must be controlled in such a way that the total charge delivered in every stimulation cycle is zero in order not to cause possible irreversible biological reactions over the electrode-tissue interface. Hence, a final block is required for charge-balancing.
Secondly, as already explained in the device specification, the waveform of burst stimulation should mimic the burst firing of the nervous cells. Their burst firing comprises a period in which the cell membrane potential hyperpolarizes following the last action potential.
For these reasons, both the stimulation waveforms include an interval in which the current polarity is reversed. It is possible to reverse the polarity of the two output currents of the current mirror via an array of switches per output, arranged in a configuration called *H-bridge*. Fig. 5.12 shows the H-bridge configurations used in the design of the multi-modal stimulator.

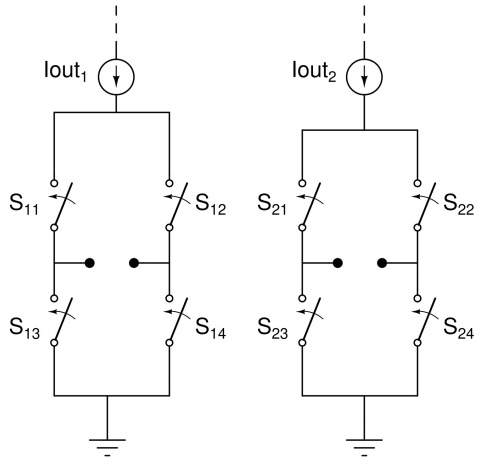


Figure 5.12: Final output stage in the current generator of the multi-moda stimulator based on 2 H-Bridge configurations

Every H-bridge circuit is characterized by 4 switches and the corresponding switches of the two configurations are controlled together. If the H-bridge at the left side of the figure is examined, whenever S_{11} and S_{14} are turned on, the output current I_{out1} flows through the shorts generated, passing through the load (which is connected between the two electrodes represented by full circles) from left to right, and then flows to the ground; if instead S_{12} and S_{14} are activated, I_{out1} flows again to the ground but this time through the load in the opposite direction.
The control signals for the switches are generated via the digital outputs of the microcontroller. The high clock frequency of the microcontroller ensures that all the switches can be turned on or off without delay (e.g. in Arduino Uno each instruction such as turning high a digital voltage requires 62 ns).
There are several ways to implement the switches. A common solution is to use N-channel MOSFETS: the switch is turned off when the MOSFET is working in cut-off region, while it is turned on when the transistor is in its triode region. In this case, the digital voltages generated by the microcontroller are used to adjust the gate voltage of the transistor. A careful selection of the transistors must be done due to the fact that they

are generally characterized by a high threshold voltage that may be greater than the operating voltage of the microcontroller. Moreover, each H-bridge would require 4 transistors, hence a total of 8.
To reduce the total form factor, the switches have been implemented by means of two dedicated quad analog switch integrated circuits. Important in the selection of the ICs are:

- the possibility to operate from a 20 V single supply (equal to the compliance voltage) and a rail-to-rail signal handling;
- a low ON-resistance that should not affect the output current;
- HIGH digital voltage (to change the status of the switches) and logic power supply should be compatible with the operating voltage of the microcontroller;
- fast turn on and turn off time, that do not introduce a delay that could alter the stimulation waveform.

Finally, the analog switch IC that has been selected for this application is the MAX313.

5.3. Microcontroller

The microcontroller is the core of the multi-modal stimulator. Programming a microcontroller is essential in basically all the aspects of this design. In this application the microcontroller is used for the following tasks:

- Communication with the external memory storage;
- Communication with the user interface;
- Generation of the stimulus waveform (through pulse width modulation and through the control of the analog switches);
- Generation of the audio signal.

Based on these, the microcontroller needs to fulfill the following requirements:

1. it must be possible to power it via a 3.7 V or 9 V battery;
2. it must support serial communication with an external SD card;
3. it must be able to read audio .WAV files;
4. it must contain at least 3 PWM output pins: one is used for DC/burst waveform generation, one for low noise, and one for the audio signal generation;
5. it must contain several digital output pins to control the switches (and to set a logic voltage required by some ICs to work);
6. it must be possible to modify the PWM frequency of its timers to a value high enough to limit significantly the voltage ripple at the output of the PWM DAC (according to Eq. 5.15) ;

7. its dimensions must be as small as possible in order to reduce the dimensions of the multi-modal stimulator and it has to be lightweight;

8. its clock speed must be fast enough to handle all the operations. Especially, a stereo 8 bit audio file with a sample rate of 16000 Hz must be read with sufficient speed. The Flash memory must have enough space to store the program required by the functioning of the multi-modal stimulator;

9. A battery-powered application requires a microcontroller that does not consume too much power.

The use of 8 bit audio files and the PWM technique for audio signal generation (that will be discussed in the chapter "Circuit for acoustic stimulation") eliminates the need of a microcontroller with a very powerful processor addressed for music applications such as the SAMD21 present in the Arduino MKR Zero.
The basic architecture combined with a lower power consumption and lower dimensions led to the final selection of the Arduino Uno board over BeagleBone Black and Raspberry Pi.
The specifications of the Arduino Uno board are shown in table 5.2.

Microprocessor	ATMEGA 328P
Operating voltage	5 V
Supply voltage	7-12 V
Digital I/O pins	14
PWM pins	6
max DC current per I/O pin	20 mA
Flash memory	32 KB
Clock speed	16 MHz
Dimensions	68.6 mm X 53.4 mm
Weight	25 g

Table 5.2: Technical specifications of Arduino Uno board [125]

The Arduino board is easily programmable via the Arduino Integrated Development Environment which is based on a high-level programming language derived from C and C++ provided with an enormous number of libraries that makes it very simple to program the microcontroller. In particular, two Arduino libraries are important in the implementation of the multi-modal stimulator: the SD and the TMRpcm libraries, respectively used for interfacing the SD card and to read a .WAV file and to generate an audio signal.
One feature that is important to discuss here is the architecture of the timers present in the microprocessor ATMEGA 328P. A good knowledge of the their architecture is required to set the PWM frequency to the desired speed.
In the Arduino Uno, each Timer is controlled by a 16 MHz external quartz clock. The Timer is a counter that increases its count every 62 ns until a maximum value is reached, after which the Timer resets. Due to the high speed of the clock, an intermediate module is present between clock and Timer, the prescaler. Thanks to the prescaler, the Timer skips some clock cycles according to the value set on the prescaler, thereby reducing its operation frequency. When the prescaler is not activated, its value is 0 and no clock signal is passed to the Timer; otherwise, the prescaler value can be set to 1, 8, 64, etc. Obviously, the Timer frequency is inversely proportional to the prescaler value N:

$$F_{timer} \approx \frac{F_{clock}}{N} \tag{5.31}$$

The registers which are used to control the timers are:

- TTCCRxA and TTCCRxB (where x = 0, 1, or 2 depending on the timer, and A and B is for the the first or second PWM output) - Timer/Counter Control Registers: their bits encode the timer characteristics (e.g. prescaler value, PWM mode, etc);
- TCNTx - Timer/Counter Register: controls the count of the Timer;
- TIMSKx - Timer/Counter Interrupt Mask Register: generates a flag or interrupt when the maximum value is reached by the Timer;
- OCRxA and OCRxB - Output Compare Registers;
- TIFRx - Timer/Counter Interrput Flag Register.

The ATMEGA 328P allows for the choice of two PWM modes.
In the FAST PWM mode, the Timer counts increasingly from 0 to 255, and HIGH PWM output is generated whenever the Timer completes the count and restarts from 0, while the output is set to LOW when the timer arrives to the position of the value contained in the OCRx. Besides the prescaler, in the Fast PWM mode the PWM frequency is also inversely proportional to the number of cycles the Timer takes to reset which is determined by the value of the OCRx register:

$$F_{timer} = \frac{F_{clock}}{N \cdot k} \tag{5.32}$$

where k is the value of the OCRx register.
The second possibility is the Phase-Correct PWM. The Timer counts from 0 to 255 and then it does not reset but

goes back from 255 to 0. The PWM output turns LOW when the Timer increases from 0 to the value of OCRx and then turns HIGH when it arrives to the OCRx in the way to come back. The PWM output of Phase-Correct PWM is more symmetrical, however the frequency is halved due to the bidirectional count of the Timer:

$$F_{timer} = \frac{F_{clock}}{2 \cdot N \cdot k} \tag{5.33}$$

In order to reduce the voltage ripple at the output of the PWM DAC, the PWM frequency must be chosen as high as possible. For this reason it is both important to set the correct values in the Timer registers in order to enable Fast PWM, both to set the mimimum prescaler value allowed, and to reduce as much as possible the value contained in the OCRx register because the default one is 255. The value of OCRx must be chosen according to the precision of the output current of the multi-modal stimulator. Taking into account that the precision in terms of voltage must be 100 mV and that the operating voltage is 5 V, the total number of output levels must be 50 (from 0 to 5 V, with a step size of 100 mV), meaning that the OCRx must be set to k = 50. If the minimum prescaler value N = 1 is chosen, the PWM frequency becomes F_{PWM} = 320 kHz. As a consequence, the output of the PWM DAC will have a ripple of only approximately $V_{ripple} \approx$ 17 mV.

5.3.1. Architecture of the ATMEGA 328P Timers

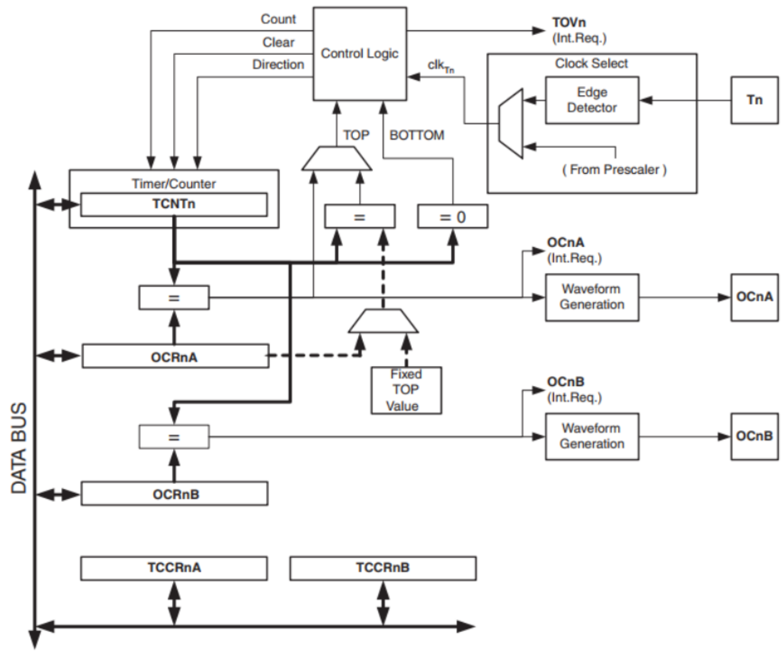


Figure 5.13: Architecture of the ATMega328 Timer 0 present in the Arduino Uno [22]

The microcontroller Arduino Uno contains three Timers, each one of them capable of generating 2 PWM signals. Timer 0 and Timer 2 are 8 bit Timers, while Timer 1 is a 16 bit architecture, which however generates PWM outputs with an 8 bit duty cycle resolution.

All the Timers are composed of several units. The Clock Select logic block manages the clock source of the Timer (either internal via the prescaler or external) and contains an edge detector used to increase the value of the Timer. The clock source is chosen via modifying the Clock Select (CS) bits that are contained in the register TTCCRxB. For instance, if a prescaler of N = 1 needs to be selected, the bits must be set to CSx2 = 0, CSx1 = 0, CSx0 = 1. The signal coming out of the Clock Select logic block is called timer clock clkTx.

The main part of each Timer is the Counter Unit. At each timer clock clkTx, the value contained in the Timer register TCNTx is refreshed according to the inputs sent by the Control Logic. The input "count" increases or decreases the value by 1, "direction" determines if the TCNTx must be incremented or decremented, while "clear" refreshes the value. When the TCNTx has reached the minimum or maximum value, a signal is sent to the Control Logic (the inputs "bottom" and "top" in the picture). The counting sequence and therefore the PWM mode is controlled via the Waveform Generation Mode bits WGMx of the registers TTCCRxA and TTCCRxB. Fast PWM with the possibility to modify the maximum value of the Timer register is set with WGMx2 = 1, WGMx1 = 1, WGMx0 = 1.

The Output Compare Unit contains a comparator which constantly compares the values contained in the TCNTx and in OCRxA or OCRxB. When the two values are the same, a match signal is generated by the comparator and sent to the Waveform Generator which in turns produces an output (according to the signals received by other registers, which deal with characteristics of the PWM mode), that is encoded in the Output Compare register OCAx or OCBx.

Finally, in the last block, called Compare Match Output Unit, the output value contained in the Output Compare register must reach the output pin. In order to do this, the Compare Output Mode bits (in case of Timer 0 the register containing the bits is the COM0x1:0) must be enabled. Once enabled, the Output Compare state is overwritten on the output pin when the Data Direction Register (DDR) is set to "output" (indeed, the DDR decides if the OCAx or OCBx must be written in the input or output port) [22].

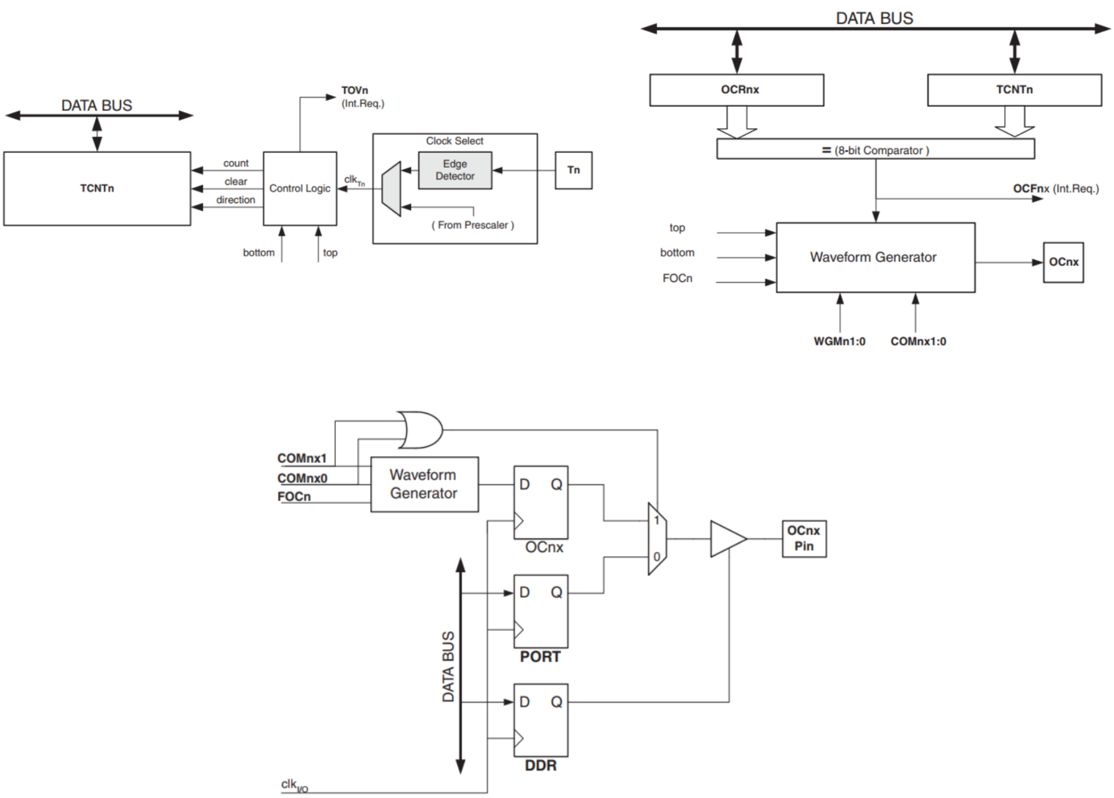


Figure 5.14: Blocks composing the Timer 0 of ATMega328: Counter Unit (top left), Output Compare Unit (top right), and Compare Match Output Unit (bottom) [22]

5.4. Circuit for acoustic stimulation

As mentioned in the section "Microcontroller", the generation of an acoustic signal is possible using the PWM function of the microcontroller. After the header, that contains information regarding the sample rate and the length of the data, each sample of the .WAV file is interpreted by the microcontroller as a duty cycle for PWM. In the Arduino Uno context, a data sample is read from the micro SD card and the value of the OCRx register is updated with the value encoded in that sample every interval $t_S = \frac{1}{F_{SAMPLE}}$, where F_{SAMPLE} is the sampling rate of the .WAV file. In this way, in every interval t_S the duty cycle of the PWM signal is updated, while the PWM frequency is kept constant.

In order to make the PWM audio playback possible, the audio format is important. The resolution of the .WAV file must not exceed the duty cycle resolution of the microcontroller. In Arduino Uno the duty cycle resolution is 8 bit, meaning that, after being properly low-pass filtered, a PWM signal can generate a total of 256 (= 2^8) analog values. Moreover, an "unsigned" PCM format is required. A standard "signed" format would mean that the data samples can assume both positive and negative values, and therefore could not be associated with a PWM duty cycle.

Due to limitations in the processor capacity of Arduino Uno, the sample rate has to be lower than the standard 44100 Hz. Following the Nyquist theorem, in order not to loose information from the audio signal, the sampling

rate should be at least double the maximum frequency of the signal. This means that if F_{SAMPLE} < 44100 Hz, not all the frequencies in the audible spectrum will be perceived. Fortunately, the audio signal will be only composed of a sequence of pure tones that have a frequency around the tinnitus one, that hopefully should not be higher than a few thousands Hz.
Finally, the .WAV file will have the following characteristics:

- Audio format: unsigned PCM;
- Resolution: 8 bit;
- Sample rate: 16000 Hz (or 8000 Hz);
- Number of channels: 2 (stereo).

At this point, a PWM DAC would be required to filter the unwanted harmonics of the PWM frequency and to obtain a proper analog signal. However, if the PWM frequency is set to a value higher than 20000 Hz (the upper limit of the hearing range), a low pass filter is not needed anymore: indeed, the auditory system can be modelled as a low pass filter with a cut-off frequency of 20000 Hz and a huge roll-off, that hence will filter out the PWM frequency harmonics. Hence, the circuit design of the sound generator does not include a PWM DAC.
The circuital design of the sound generator is shown in Fig. 5.15.

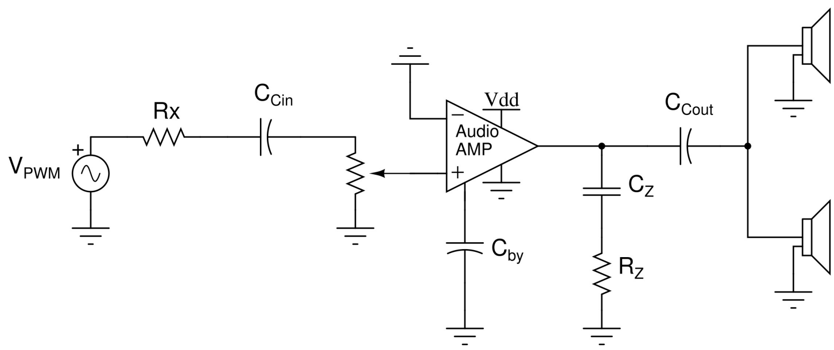


Figure 5.15: Circuital design of the sound generator

The main component of the circuit is the *audio power amplifier*. An audio power amplifier is used to bring the audio signal to a level high enough to drive the earbuds. Essential in the choice of the audio power amplifier is that its output power must be sufficiently high to be able to generate a loud sound into the earbuds (of course, the level of the sound depends also on the impedance and sensitivity of the earbuds). Then, the power amplifier must be powered from a single-supply voltage source with a voltage that matches the one of the battery used. Moreover, it must be a mono amplifier, meaning that it must be suitable for a mono audio input signal. Again, it is fundamental a limited power consumption, small enough to be included in the design of a portable device. The audio quality is not the primary goal of the multi-modal stimulator but it is also important that the amplifier presents good performances in terms of PSRR, THD + N, and SNR. Finally, it is necessary that the audio amplifier has a passband large enough to handle the fast transients of the PWM signal. In the end, the mono audio power amplifier LM386 has been selected: it has a wide supply voltage range (4-18 V), low power dissipation (if powered from 9 V, it should dissipate a maximum of about 500 mW), large passband (cut-off frequency around 100 kHz), and low distortion. Furthermore, compared to other audio amplifiers, the LM386 requires a small number of external components.

The other components present in the figure have been chosen according to the specifications of the amplifier. A high resistance Rx is used to drop the 5 V PWM input signal down to a level within the amplifier input range (which is [-0.4;0.4 V]). The coupling capacitor C_{Cin} removes the unwanted DC component present in the input PWM signal. After that, an analog potentiometer ensures a proper adjustment of the input PWM voltage, and therefore provides volume control. The bypass capacitor C_{by} is connected between the proper pin of the integrated circuit and ground to remove the AC noise introduced by the power supply: the reactance due to the bypass capacitor is inversely proportional both to the frequency and to the capacitance ($X_{Cby} = \frac{1}{2\pi f \cdot C_{by}}$), suggesting that a high capacitance value should be necessary to properly filter the low frequencies and so to maximize the PSRR across the entire frequency spectrum. At the output of the audio amplifier, a coupling capacitor and a filter are present. The output coupling capacitor C_{Cout} removes possible DC offset introduced by the power supply or the internal circuitry of the amplifier. A high value is important in order to properly preserve all the frequencies in the hearing range. Finally, as it often happens in the design of audio power amplifiers, the datasheet suggests to implement an RC series connection between the output terminal and ground; this electrical network is called Boucherot cell and is an electronic filter which is employed in audio application to damp high frequency oscillations. Moreover, a speaker contains an inductive component that tends to attenuate the high frequencies of the audio signal (indeed, the reactance of an inductor is $X_L = 2\pi$ f L): the Boucherot cell compensates the inductive reactance so that the output load becomes purely resistive.

According to the explanations given above, the value of the components of the sound generator are Rx = 100 kΩ, C_{Cin} = 10 μF, C_{by} = 10 μF, C_Z = 0.047 μF, R_Z = 10 Ω, C_{Cout} = 220 μF, and a 10 kΩ potentiometer.

5.5. Power management

The multi-modal stimulator is a portable device, thus needs to be battery-powered. The choice of the battery voltage depends on the operating voltage of the microcontroller. Arduino Uno operates at 5 V, meaning that the battery required should provide a sufficiently high voltage supply. A series of two 3 V batteries would provide a powering voltage of 6 V. That would be a risky solution due to the fact that during operation the batteries discharge leading to a drop in their voltage which could rapidly go below the operating voltage of the microcontroller. Following the recommendation of the developers, the voltage provided by the battery should be between 9 and 12 V. Higher voltages may be also used but the power delivered could overheat the board.

Due to the device requirements, a high-voltage power supply is necessary to power the current mirror.

One design solution may be to connect some batteries in series in such a way that the total voltage generated is equal or higher than 20 V. Then, an LDO regulator may be used to step down the voltage to a suitable value for the microcontroller, the OPAMPs, and the audio amplifier (that could be 9 V). Of course, the main drawback is that it would not be efficient in terms of space consumption.

The most reasonable idea is to use a 9 V battery as low-voltage power supply and to generate a high-voltage supply for the current mirror and the analog switches through a *boost converter*.
The general architecture of a boost converter is depicted in Fig. 5.16: it contains an inductor, two capacitors, and two switches.

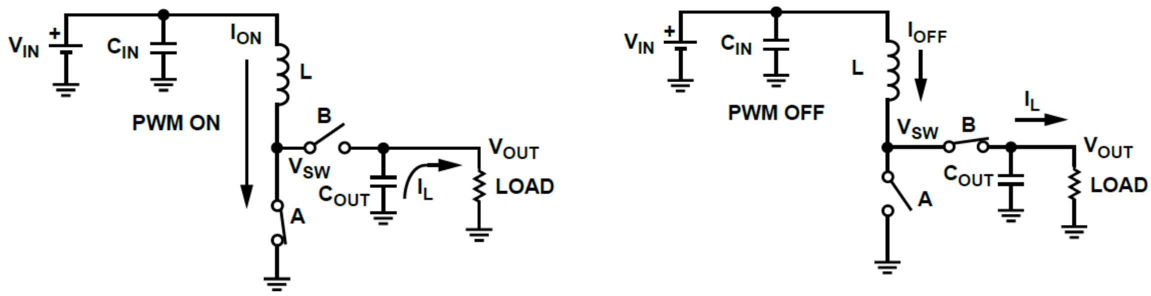


Figure 5.16: Architecture of a boost converter: boost converter working in phase 1 (left) and boost converter working in phase 2 (right) [75]

The key element is the inductor that is used to alternatively store and release energy at a different voltage. In the first phase of operation (Fig. 5.16, left), switch A is turned on while switch B is turned off. In this way, the current drained from the battery flows across the inductor and towards the ground. Due to the positive voltage across the inductor, the current starts growing, consequently charging it. In phase 2 instead the status of the switches is reversed; as a consequence, the current from the battery conveys to the load. The negative voltage over the inductor brings to the decrease of the current and the energy stored in the inductor is delivered to the load.
The operation of the boost converter is regulated by a PWM signal: the voltage HIGH is associated with phase 1, while voltage LOW with phase 2. The output voltage is dependent on the duty cycle D of the PWM signal via the following equation:

$$V_{OUT} = \frac{V_{IN}}{1 - D} \tag{5.34}$$

Hence, in order to obtain a 20 V output voltage from a 9 V battery, the duty cycle of the PWM signal must be D = 55%.
At the same time, the PWM frequency determines the output voltage ripple and the power consumption of the boost converter: the higher the frequency, the higher is the power consumption, but also the lower is the ripple (big inductors are required to have a small ripple if the PWM frequency is low). Normally, low power boost converters works with a PWM frequency lower than 2 MHz.
Due to the energy conservation, the input power must be equal to the output power in a boost converter. Therefore, a simple calculation of the battery current drain can be done (excluding possible power losses) through:

$$I_{drain} = \frac{V_{OUT} I_{OUT}}{V_{IN}} \tag{5.35}$$

Considering that the output current is the sum of the currents flowing through the three PNPs of the current

mirror, the current drain $I_{drain} \simeq 13$ mA, if the programmed current of the multi-modal stimulator is 2 mA.
A bypass capacitor C_{IN} is connected in parallel with the battery to filter the AC noise, while the output capacitor C_{OUT} is used to reduce the voltage ripple [75].
In this design the dedicated integrated circuit MT3608 has been used to implement the boost converter. The IC contains a PWM generator and an internal MOSFET which implements switch A. In addition to the input, output capacitor, and the inductor, a Schottky diode is used as an output rectifier to implement switch B. Finally, the IC requires a proper selection of the values of two resistors to adjust a reference voltage in order to obtain the desired output voltage (the upper limit is 28 V).

6

Device design: software

After presenting the analog design of the multi-modal stimulator, the next step is to create the proper signals for stimulation and to write the code that is necessary to guide the microcontroller operations.

6.1. Digital sound processing

Digital sound processing (DSP) is fundamental both for the realization of a "noise + DC" electrical stimulation and acoustic stimulation. DSP is used to create a customized stereo digital signal and to convert it to proper format so that it can be read and output by the microcontroller. The software Audacity is perfect for this purpose. The requirement for this application is to reproduce a digital signal made of two components: one characterized by the repetition of pure tones having frequencies around the tinnitus one and the other must be a noisy signal with a spectrum included in the interval 0.01-100 Hz. Of course, the tinnitus frequency varies from patient to patient, therefore the first component of the signal has to be updated from time to time.
An example of stereo signal that has been created is depicted in Fig. 6.1. 200, 500, 600, 700, 800, and 900 Hz sinusoidal tones are randomly sorted. Each one lasts 1 second and is followed by a silent period of 1 second to obtain an intermittent acoustic stimulation. The second signal is made by a digitally low-pass filtered white noise with a cut-off frequency of 100 Hz (roll-off 48 dB).

Finally, the stereo audio track is saved into an .WAV file with the proper sample frequency, resolution, and format.
A .WAV file contains two main parts: the header and the raw data. The header describes the characteristics of the audio signal encoded in the file: 44 bytes are present to define file format, audio format, number of channels, and sample rate, respectively. After these 44 bytes the samples of the signal follows (in unsigned 8 bit PCM each sample is made of a single byte encoding a decimal number between 0 and 255). Hence, the microcontroller will

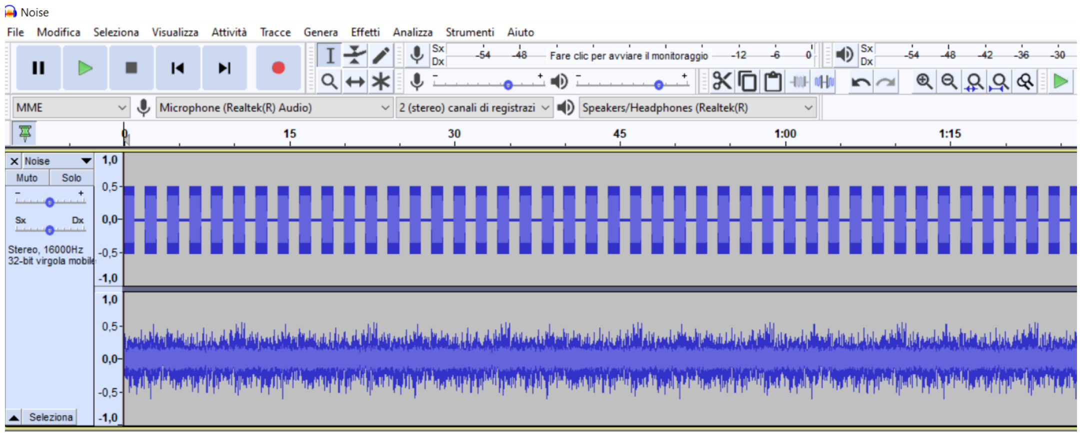


Figure 6.1: Stereo track generated in Audacity: the signal on top is the sequence of tones, while the one at the bottom is the noisy signal

have to read all the bytes, discard the header, and output "feed" the PWM circuit only with the bytes containing the samples.

6.2. Programming the microcontroller: algorithm for synchronous multi-modal stimulation and sound generation

The operations required to program the microcontroller are in the following order:

1. Activate the serial communication;
2. Insert the stimulation parameters through the programming interface;
3. Read and save the input values into appropriate variables;
4. Define two variables , e.g. "timer" and "end", for counting the time;
5. Adjust the values of the PWM registers to set the desired PWM parameters;
6. Initialize the necessary output pins for electrical and acoustic stimulation;
7. Initialize serial communication with the micro SD card;
8. Set the sample rate (i.e. the PWM frequency) for the audio signals;
9. Begin audio data acquisition and playback (bytes acquired from the file are alternatively output to OCR1A and OCR1B, the output PWM registers of Timer 1);
10. Deactivate second pin for audio playback (only for burst stimulation: no need for stereo playback and so one audio output has to be disabled otherwise an unwanted signal enters the summing amplifier);
11. Generate the burst/"noise + DC" waveform (with proper switches control);

12. Set intermittent electrical stimulation: repeat the bursts until the variable "timer" equals the total time length of each sound tone, then disable the pin for burst stimulation for the same time length. Iterate this process (only for burst stimulation);

13. Once the variable "end" has the same value of the length of the audio track (i.e. the audio signal is finished to be reproduced), return to point 9.

In the first prototype of the multi-modal stimulator, the serial monitor of the Arduino Uno will be used as user interface.
The variable "timer" is very important to determine the stimulation time and to allow for intermittent stimulation. Of course, intermittent stimulation is only present in burst stimulation, where the electrical and acoustic stimulation must intermittently and synchronously be enabled and disabled for few seconds. The "timer" variable is updated every burst period and it is reset whenever the tone is stopped in acoustic stimulation. In the other therapy, based on tones paired with "noise + DC" stimulation, intermittent stimulation is meant to be applied only over the audio signal and the duration of each cycle is set by the audio signal itself (composed of repetitions of tone + silence).
Through the SPI communication between the microcontroller and the micro SD card the 8-bit audio samples are progressively stored into the Arduino data buffer.
The audio playback through the PWM pin in Arduino is realized by means of the library TMRpcm: it permits to read step by step the bytes encoding the audio samples from the .WAV file and to treat them as duty cycles to update the PWM signal. The PWM frequency represents the frequency used to sample the audio data and should be at least twice the sample rate of the audio file for a proper sampling. The audio playback algorithm is based on the Timer interrupt: a special function called interrupt service routine (ISR) is used to interrupt the CPU and to update the value of the output PWM registers OCRxA and OCRxB at regular intervals dictated by the PWM frequency. In this way, the ISR function allows to continue to run the Arduino program while going on with the playback, enabling the simultaneous acoustic and electrical stimulation. As a consequence, the time delay between the onset of the acoustic and electrical waveforms is only limited by the time resolution of the microcontroller, which is 62 ns.
The audio signals are sent to Pins 9 and 10, which are controlled by Timer 1. Timer 1 is the best choice in this sense because it is a 16-bit timer and its registers, therefore, can store a bigger amound of bits compared to an 8-bit one: in case of stereo audio file, it allows to write two consecutive bytes in the two output registers OCR1A and OCR1B without delay. Moreover, Timer 0 and 2 are not recommended to be used because are necessary for the basic timer functions (e.g. the function *delay()* is used to interrupt the execution of the code for a specified period of time, and is necessary for generating the desired waveforms for electrical stimulation) and for serial communication. A better audio signal is obtained setting the Timer 1 PWM frequency to the Phase-Correct PWM mode, which results in a lower harmonic distortion than the Fast-PWM mode
The waveform generation is made possible by turning HIGH and LOW the digital outputs used to control the switches. Their timing is dependent on the stimulation parameters (spike frequency and burst frequency for burst stimulation, phase duration for "noise + DC" stimulation).

7

Validation tests

Once the design is concluded and the components are properly selected, the circuit is implemented. Two separated PCBs are realized: one in which the components for the current generator are assembled and one for the sound generator.
Eventually, several validation tests are performed in order to assess the functionality of the circuits, especially of the current generator.

7.1. Measurement setup

The measurement setup is composed of the following equipment:

- Computer Dell Precision 5530, Intel Core i7, 2.60 GHz;
- PC Oscilloscope Hantek 6022 BE;
- Digital multimeter GBC KDM 120;
- Breadboard general purpose Adafruit Industries;
- Arduino Uno Rev3;
- Micro SD card module for Arduino;
- 9 V battery Energizer Max with a battery snap connector;
- Jumper wires;
- 3.5 mm stereo female jack in mono configuration;

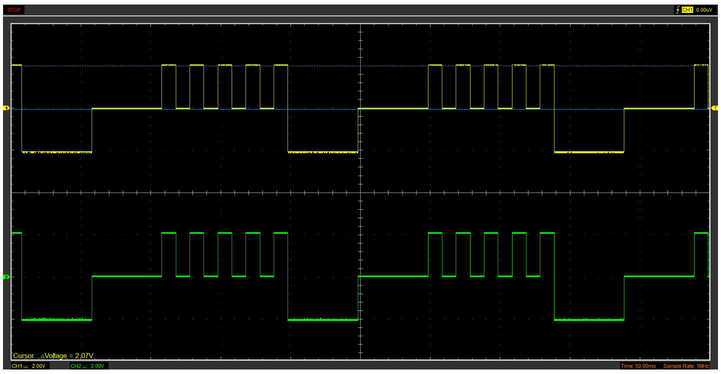
- Apple earbuds.

The multimeter and the PC Oscilloscope is used for measuring the output signals. In particular, the oscilloscope has the functions of plotting the waveforms of burst and "noise + DC" stimulation and determining the synchronization between the acoustic and the electrical stimulation. On the other hand, the accuracy of the DC outputs and the power consumption are measured using the multimeter.
The breadboard is used to electrically connect the 9-V battery to the microcontroller and to the other circuits, and also to connect the output loads to the output pins of the current generator.
The SD card module is properly connected to the required pins of Arduino, and the inputs for the current generator are taken from Pin 3 (for the DC/burst amplitude) and Pin 9 (for the noise). Moreover, the digital Pins 6, 7, and 8 are used to control the analog switches. Pin 10 of the Arduino serves as the input for the sound generator.
Finally, the output and ground of the sound generator are attached to the wires of the female jack. A stereo female jack is used: one wire has been soldered to ground, while the other two have been merged together in order to get a mono sound output in both the speakers of the earbuds.

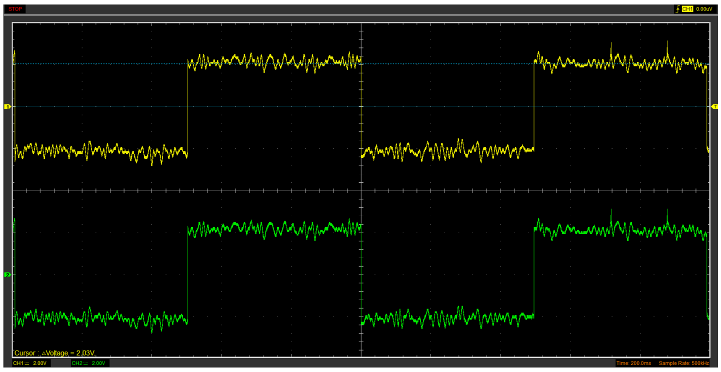
7.2. Stimulation waveforms and frequency spectrum of "noise + DC" waveform

The first test performed is to assess the validity of the waveforms both in case of burst and "noise + DC" stimulation. A first prototype of the PCB containing the current generator is used, which does not include the boost converter. The latter is connected to the PCB via the breadboard, as well as the 9-V battery to power the circuit. Afterwards, jumpers are used to directly connect the current generator to the Arduino. Pin 9 is used to generate noise, Pin 3 to generate the DC, and Pins 6, 7, and 8 are used to digitally control the analog switches (Pin 8 is used to generate the logic supply voltage). The Arduino is also powered by the battery. Eventually, two 1 kΩ resistances are soldered between the output terminals to simulate the loads.
Both the probes of the PC Oscilloscope are attached to the four terminals of the loads. The voltage across the two resistors are measured and then the output currents are determined.
The outcomes of the test are shown in Fig. 7.1a and Fig. 7.1b.

The burst stimulation waveform is obtained by setting the output voltage at Pin 9 to 0 V and controlling the output voltage at Pin 3 for setting the current amplitude. The change of polarity and the control of the burst and spike frequencies are possible by turning the analog switches on and off with the correct timing.
The two outputs have the same waveform and are perfectly synchronized, and are therefore perfectly suitable for bilateral stimulation.
On the other hand, the "noise + DC" stimulation waveform is obtained by the creation of an stereo audio file where the channel used for electrical stimulation is formed by a white noise signal strongly low-pass filtered (with a roll-off of 40 db) with a cut-off frequency of 100 Hz. The output of Pin 3 is regulated according to the programmed DC current, while Pin 9 is used to output the samples of the noisy signal read from the audio file.



(a) Waveform of burst stimulation (F_{spike} = 50 Hz, F_{burst} = 5 Hz, programmed current amplitude I = 2 mA)



(b) Waveform of "noise + DC" stimulation (pulse width 500 ms, programmed DC current I = 2 mA, noise frequency spectrum 0.01-100 Hz)

Figure 7.1: Stimulation waveforms of the multi-modal stimulator visible in the PC Oscilloscope

Unfortunately, due to the limitations of the PC Oscilloscope, it is not possible to generate a "noise + DC" signal with a phase duration included in the range imposed by the device specifications (several seconds). Also in this case, the change of polarity is realized by correctly timing the outputs of Pins 6 and 7.

In addition to the waveform, with the same set-up another acquisition is taken. A "noise + DC" signal is generated with a constant polarity and a DC amplitude I = 2 mA. The waveform samples for an observation time of 10 s are saved and visualized in Matlab. Then, the frequency spectrum of the signal is determined, and is shown in Fig. 7.2.

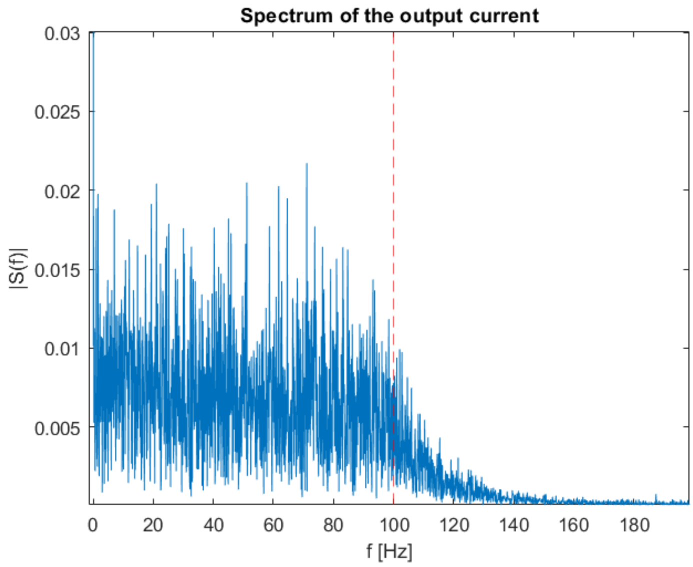


Figure 7.2: Frequency spectrum of the "noise + DC" output signal

From the power spectral density it is clearly visible that the frequencies higher than 100 Hz are strongly attenuated as desired. All the frequencies below 100 Hz are present and the maximum power of the signal corresponds to 0 Hz, which is indeed the frequency of the programmed DC offset.

7.3. Accuracy of the DC output current

Both the DC offset for "noise + DC" stimulation and the current amplitude of the burst stimulation should have an error which must not exceed the precision of the output specified by the requirements. In particular, in order to be considered accurate, the DC current for both the output channels of the current generator should not contain an error greater than 0.1 mA.
The accuracy is measured by varying the programmed current from 0 to 5 mA and using two resistive loads of R_{load} = 1 kΩ. The voltages over the two resistances have been measured with the digital multimeter.
The plot representing the results is shown in Fig. 7.3.

The same tests are conducted using two different PWM frequencies, 160 kHz and 320 kHz, and, unexpectedly, the most accurate results are obtained with the lower frequency. As it is visible, both the output currents have a steady trend which deviates from the ideal line of a maximum of 0.06 mA (Fig. 7.4. Also the error between the two output currents does not exceed 0.01 mA, meaning that a precise and equal bilateral stimulation is possible with the multi-modal stimulator.

The two main sources of error are found to be the imprecise PWM output of the Arduino pins and consequently the digital-to-analog conversion, and the current mirror, which may be for instance suffering a bit from the Early effect. The Early effect could be reduced by adding a cascoding configuration.
The mismatch between the ideal and the real output currents does not change until 5 mA of programmed current (which is the maximum programmable due to the limit of the Arduino operating voltage) but, on the

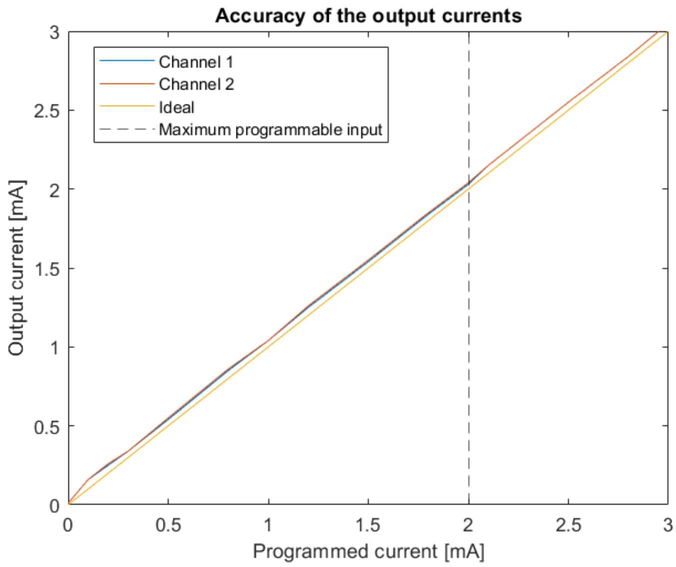


Figure 7.3: Output currents as a function of programmed input in the current generator (load R_{load} = 1 kΩ, F_{PWM} = 160 kHz)

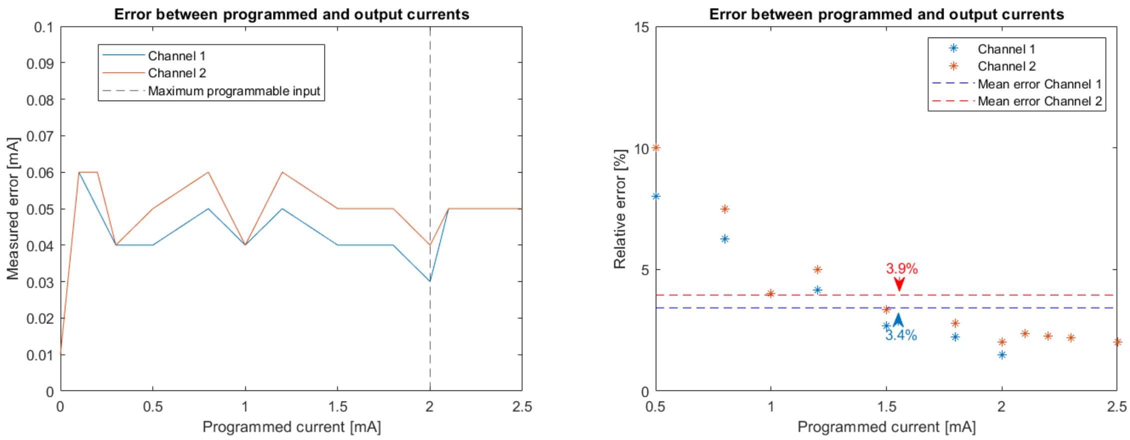


Figure 7.4: Measured errors of the output currents with respect to the programmed input

contrary, for values higher than 2 mA the two output currents are almost identical (error < 0.01 mA). Consequently, in future developments the multi-modal stimulator could be programmed in order to deliver up to 5 mA of DC current.

Later on, the dependency of the output currents on the load is measured. The programmed current is set to 1 and then to 2 mA, while the twenty resistances used are ranging from 10 Ω to approximately 20 kΩ. In this case, only one output channel is considered. Surprisingly, the mismatch with the ideal current is lower when an higher input current is programmed. In both the curves present in Fig. 7.5 it does not exceed 0.06 mA until the point in which the load is assuming values beyond the limits imposed by the compliance voltage (around 9.5 kΩ).

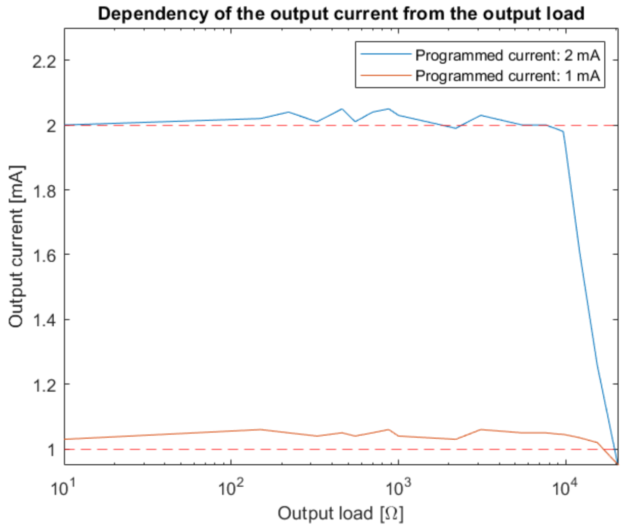


Figure 7.5: Dependency of the output currents on the load

7.4. Synchronization of current and sound generator outputs

One of the main requirements of the multi-modal stimulator is that it must guarantee a simultaneous acoustic and electrical stimulation. This means that the onset of the acoustic signal should match the one of the output current in every period of the intermittent stimulation.

The TMRpcm library is used to play an intermittent 50 Hz sinusoidal tone over the Pin 10 of the Arduino. In particular, the acoustic signal created in Audacity is composed of a 1 s tone followed by 1 s "silence". The other channel of the audio file contains the noisy signal required for the generation of the "noise + DC" waveform through Pin 9 of the Arduino. The noisy signal is also intermittent but in this case the interruptions are generated by programming the microcontroller. In a second test Pin 9 is disabled and the burst stimulation waveform is generated by programming in such a way that the intermittent acoustic and electrical stimulation signals are synchronized.

Unfortunately, it was not possible to detect when the acoustic stimulation was turned on and off due to the fact that the "silence" is encoded in the .WAV file as a value which is not zero. As a consequence, the corresponding duty cycle is not zero and therefore an intermittent PWM signal is not recognizable in the PC Oscilloscope because "silence" does not correspond to "no signal". This does not occur if the PWM signal is converted to an analog signal through a low-pass filter: when stimulation is ON, the output signal is seen as a sine wave, while, when stimulation is OFF, only the DC offset is present. Hence, for this test the sound generator is replaced by a passive first-order low pass filter of parameters R = 150 Ω and C = 10 μF, and its output voltage is visualized by the PC Oscilloscope. The delay introduced by the audio amplifier and the remaining parts of the sound generator would not differ so much from the results of the test.

The simultaneous waveforms of the acoustic signal and the electrical ones are depicted in Fig. 7.6 and 7.7. Both the figures capture the two signals in the moment in which there is the transition between stimulation OFF and stimulation ON during the intermittent stimulation.

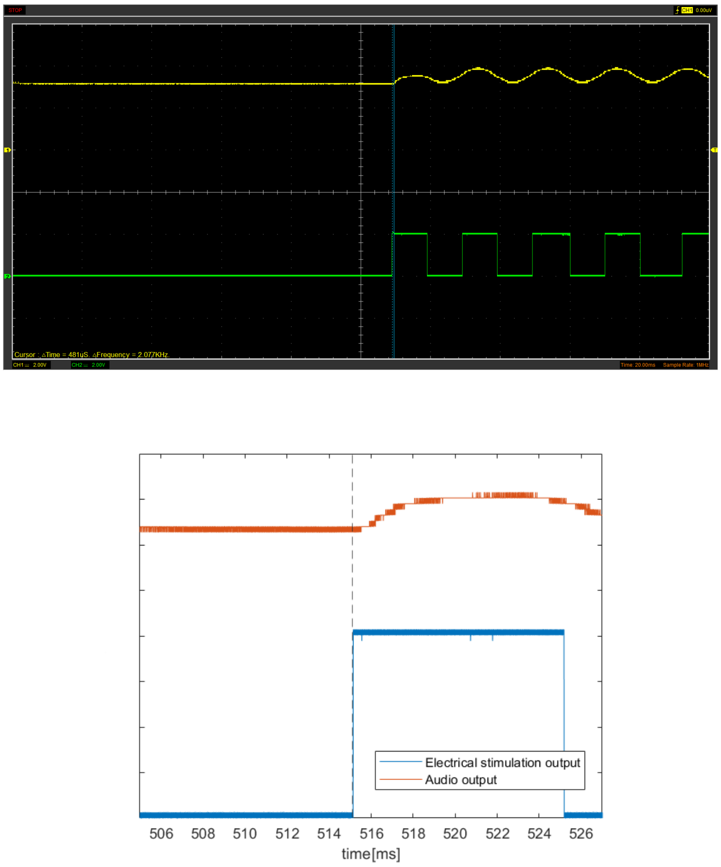
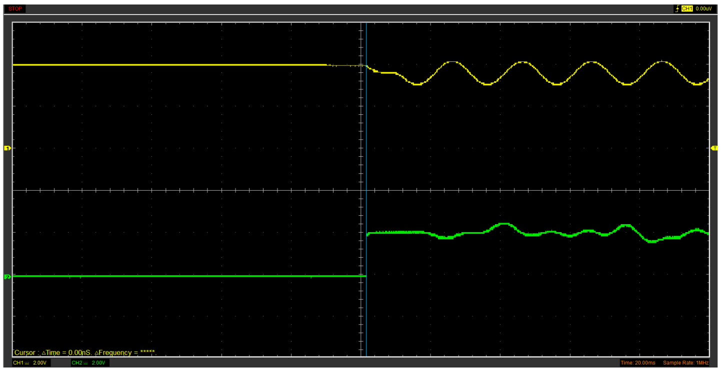


Figure 7.6: Simultaneous acoustic and burst stimulation waveforms (F_{TONE} = 50 Hz, F_{spike} = 50 Hz, F_{burst} = 5 Hz, programmed current I = 2 mA, intermittent stimulation t_{ON} = 1 s and t_{OFF} = 1 s)

The measured time delay between the onset of the acoustic and electrical stimulation signal is less than 1 ms (burst stimulation: about 700 μs; "noise + DC" stimulation: about 100 μs).



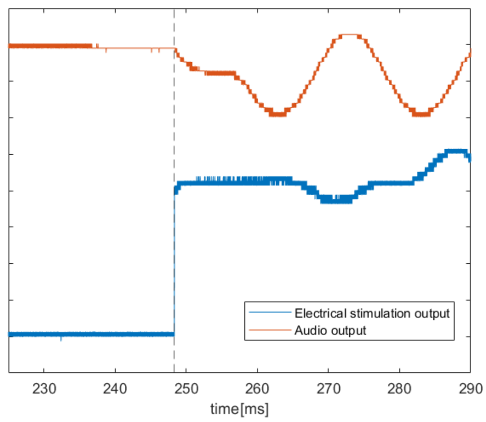


Figure 7.7: Simultaneous acoustic and "noise + DC" stimulation waveforms (last two figures, F_{TONE} = 50 Hz, programmed current I = 2 mA, intermittent stimulation t_{ON} = 1 s and t_{OFF} = 1 s)

7.5. Power consumption

The multi-modal stimulator should ensure continuous operation for several hours per day. The power consumption is evaluated both in case of burst stimulation and "noise + DC".

To simulate an intermittent acoustic stimulation, a stereo audio file is used containing in one channel a sequence of pure tones having frequencies in the range 200-900 Hz alternated to "silence" (t_{ON} = 1 s and t_{OFF} = 1 s) and in the other a noisy signal with a frequency spectrum of 0.01-100 Hz.

The power consumption of the sound generator and the current generator is tested separately by connecting the digital multimeter in series with the 9 V battery and the rest of the circuit. In the first case, the consumption measured is 45 mW in case of quiescent current (minimum volume of potentiometer) and 540 mW when the maximum volume is set by the potentiometer. The power consumption does neither include the power consumption of the microcontroller nor the power consumed due to the communication with the micro SD card.

On the other hand, the power consumed by the current generator, the microcontroller, and the micro SD card are considered all together. The power consumption is calculated for four different values of input programmed current and for three values of resistive loads.

Both the electrical therapies have a similar power consumption, which is obviously increasing when the programmed DC current is increased and when the load assumes lower values.

Assuming the worst case scenario of load R = 500 Ω, programmed current I = 2 mA, non-intermittent burst stimulation, and maximum sound volume, the overall power consumption o the multi-modal stimulator is about 1.31 W (see Fig. 7.9). This means that the device could work efficiently for around 5.5 hours if powered by a battery with a capacity of 800 mA/h.

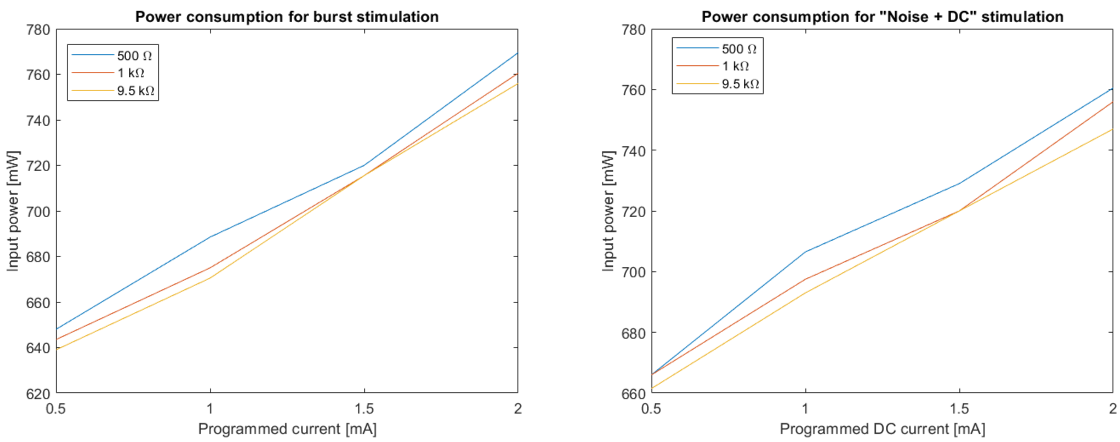


Figure 7.8: Power consumption of the current generator: (including consumption of the Arduino and the micro SD card): burst stimulation (left, F_{spike} = 50 Hz, F_{burst} = 5 Hz), "noise + DC" stimulation (right, phase duration t_{DC} = 10 s)

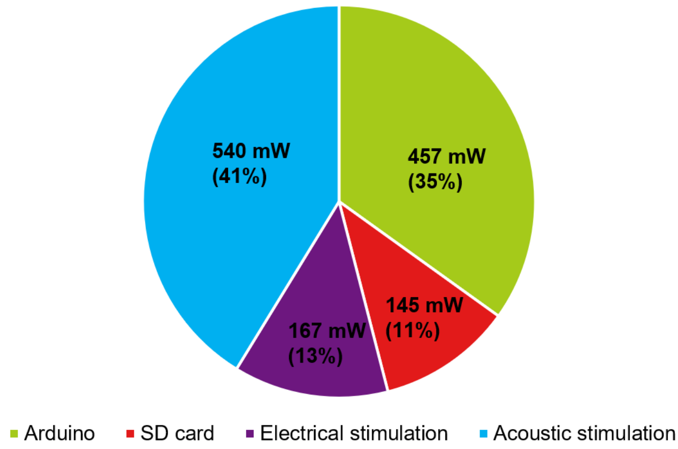


Figure 7.9: Pie Chart describing the power consumption of the multi-modal stimulator (worst case scenario: Burst stimulation with programmed current 2 mA and max audio volume)

7.6. Validation tests of the sound generator

The sound generator circuit is tested separately. The battery snap connector is soldered over the positive supply terminal and ground, and a 10kΩ linear potentiometer in the corresponding part of the circuit. Finally, a female jack in mono configuration is attached to the output and ground and a pair of Apple earbuds (approximately Z = 42 Ω impedance and 118 dB SPL/V sensitivity) are connected as a load. The input of the circuit is the PWM signal coming out of Pin 10 of the Arduino.
The .WAV file contained in the micro SD card is read and converted into an output signal on Pin 10 through the functions contained in the TMRpcm library of the Arduino. The 8-bit, 16000-Hz audio signal was composed of a sequence of pure tones of frequencies in the range 200-900 Hz with a voltage peak-to-peak of V_{pp} = 1 V, each 1 second long and separated from the following tone by a period of "silence" of 1 second (intermittent acoustic stimulation).
Unfortunately, it is not possible to justify the quality of the sound heard through the earbuds if not via a real demonstration. The audio library of Arduino allows to select two possible sampling frequencies (i.e. two PWM frequencies): 16 or 32 kHz. The higher value permits a better sampling of the audio signal and also in terms of sound eliminates an annoying background high-pitched sound caused by the fact that a 16 kHz PWM frequency is in the hearing range. The auditory system works as a low-pass filter with a cut-off of 20 kHz, therefore it is clear and experienced that the 32 kHz PWM frequency removes that background noise.
However, a background noise is noticed, which is probably introduced by the audio amplifier.
The PC Oscilloscope is used to plot the output PWM waveform. In Fig. 7.10, the output audio signal is represented in case of maximum volume (i.e. when the end-to-end resistance of the potentiometer is 1 MΩ).

Unfortunately, the output power of a PWM signal depends on the duty cycle, which is variable. However, the conditions of the test can be simulated via LTSpice. The sound generation circuit is reproduced, with an LTSpice model of the LM386 and an input sine wave of 500 Hz and V_{pp} = 1 V. The output signal is characterized by a root

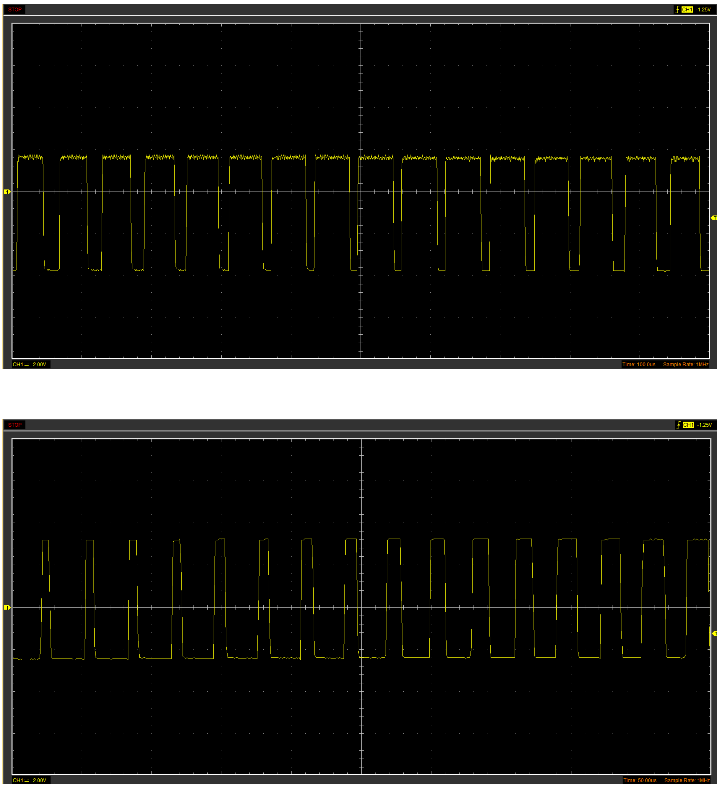


Figure 7.10: Portions of the output PWM waveform of the sound generator: output waveform with PWM frequency 16 kHz (left), Output waveform with PWM frequency 32 kHz (right)

mean square voltage $V_{RMS} \simeq 303$ mV. Hence, considering that the jack cable used is in mono configuration, i.e. the output load is represented by the parallel of the two earbuds' impedance $Z_{load} \simeq 21\ \Omega$, the output power per earbud is $P_{out} = \frac{V_{RMS}^2}{Z_{load}} \simeq 4.4$ mW. This means that with the Apple earbuds the sound intensity is higher than 110 dB SPL. Regardless of the earbuds that will be used to amplify the audio signal, the sound generation circuit is capable of delivering a very powerful audio signal, that could be heard perfectly even by people suffering from a certain degree of hearing loss. If the maximum volume is too loud, a pair of earbuds with a lower sensitivity and a higher impedance can be chosen.
Subsequently, an audio file containing a single 2000 Hz tone is stored in the micro SD card and the tone is reproduced. The PC Oscilloscope captures the samples of the audio signal for a time interval of about 130 ms and the frequency spectrum is calculated and displayed via Matlab. The frequnecy spectrum is visible in Fig. 7.11, within the frequency interval covered by the hearing range (20-20000 Hz).

As expected, the peak is covered by the 2000 Hz frequency while the noise caused by the switching frequency associated with PWM is not present (indeed, it is out of the hearing range). Some sources of noise are visible, of which the most evident are at around 13950 Hz and 17950 Hz. These are neither resulting from the performances of the audio amplifier nor by the micro SD card data exchange with the Arduino. The frequency used by Arduino to communicate with the micro SD card is about 62 Hz, while the frequencies involved in every data exchange period are way higher than 20 kHz. At the same time, the frequency spectrum of the PWM

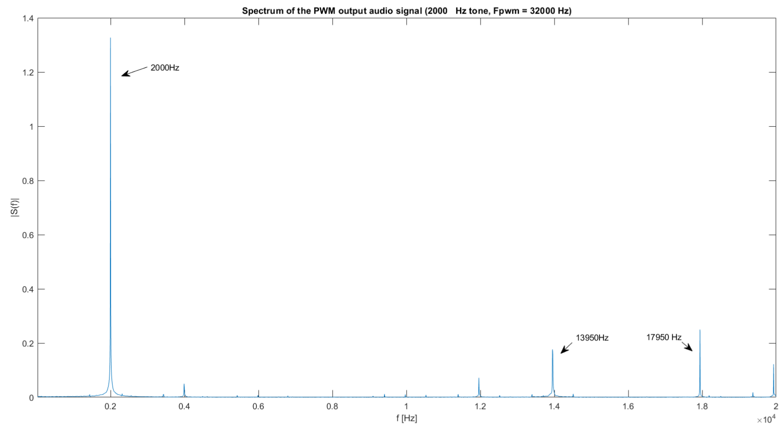


Figure 7.11: Frequency spectrum of the PWM output audio signal encoding a 2000 Hz sinusoidal tone

signal coming directly out of the Pin 10 of Arduino (and so before entering the sound generator) also contains the same main sources of noise, excluding therefore the influence of the sound generation circuit.
If the noise is considered too high and the tinnitus pitch of the patients is not too high, a good solution may be to integrate a low pass filter in the sound generator to cut the noise frequencies.
Eventually, a good recommendation would be to figure out where the frequencies originate from and how they can be avoided in a future design.

8

Conclusions and recommendations

This report describes the design of a multi-modal stimulator for the treatment of tinnitus. As explained in the literature review, there is not yet a treatment which is capable of suppressing the tinnitus for a prolonged period of time and effective for a large group of patients. However, the novel approach of multi-modal stimulation seems to steer scientists into this direction based on the consideration that multiple areas of the auditory system and non- manifest abnormalities in their electrical activity. Promising studies have been conducted and a few devices have been developed for multi-modal stimulation. A portable multi-modal stimulator that combines acoustic and electrical stimulation has not been realized yet, and this is the direction of the device explained in this report.

In collaboration with Dr. De Ridder, a list of specifications has been proposed for the design of the device, and almost all of them have been satisfied.

First of all, the multi-modal stimulator is capable of delivering two types of therapies: tinnitus-matched tones combined with burst stimulation (T1) and tinnitus-matched tones combined with "noise + DC" stimulation (T2). For both therapies, the stimulation parameters that can be set match the requirements and their accuracy is ensured. The only two exceptions are the sound frequency and the noise spectrum for "noise + DC" stimulation. In the first case, the sampling rate of the .WAV file (16000 Hz) allows for a perfect reproduction of sounds with frequencies lower than 8 kHz, meaning that the therapy does not work effectively for patients characterized by a tinnitus frequency pitch higher than that level; however, that might not be a problem since in about 64% of the situations, the tinnitus pitch does not overcome 8 kHz [86].In the second case (T2), due to the value of the coupling capacitor present in the circuit for "noise + DC" stimulation, the spectrum of the output signal contains attenuated frequencies between 0.01 and 0.07 Hz. The combined mode (T3) is not yet present in the multi-modal stimulator, but it does not imply a modification in the hardware but can be easily implemented via programming the microcontroller.

The device is programmed in such a way that intermittent stimulation is delivered as explained in Chapter 6, but it has been demonstrated that, even if a non-intermittent stimulation is applied with the most power consuming stimulation parameters and an average capacity battery of 800 mA/h, the stimulator can be used for a total duration of at least 5.5 hours. The battery type and capacity has not been decided because it depends on the stimulation duration that will be required but the multi-modal stimulation can work from any battery as long as its nominal voltage is 9 V.

The electrodes that will be used for electrical stimulation have not been defined yet and therefore a high compliance voltage is required ensuring that the desired current is delivered for high output loads. The boost converter used for generating a high voltage supply is only limited by the 660 mV voltage drop over the emitter resistors in the current mirror. In the end, the compliance voltage guaranteed by the multi-modal stimulator is slightly lower than 20 V (approximately 19.3 V).

Then, the number of channels are compliant with the device specifications: 1 channel is necessary for acoustic stimulation and 2 for bilateral electrical stimulation.

The components of the device still need to be assembled and also a proper casing has to be chosen. For this reason, it is not possible to define its final weight. However, the heaviest component is represented by the Arduino Uno microcontroller that is approximately 20 g, and therefore it is reasonable to say that the multi-modal stimulator will be lightweight and will not present a weight higher than the one imposed by the specifications. For the same reason, the dimensions cannot be specified with precision. Length and width are mainly dependent on the dimensions of the two PCBs, which are about 60 x 110 mm. The height of the device can be deduced by the height of its main components and should be around 45 mm (20 mm Arduino Uno board, 10 mm PCB with current generator and 15 mm PCB with sound generator including the battery; the micro SD card module should not influence the height too much).

Finally, the multi-modal stimulator is controlled with a computer through the serial monitor of the open-source Arduino software. The user has just to run the code and insert the stimulation parameters.

Multi-modal stimulator specifications	
Stimulation therapy	Intermittent tones + intermittent burst stimulation, intermittent tones + "noise + DC" stimulation
Stimulation waveform	Burst stimulation: current-controlled, 5 monophasic spikes per burst followed by active charge-balancing (and interburst delay dependent on burst and spike frequencies chosen); "noise + DC" stimulation: current-controlled, biphasic, selected noise superimposed on a direct current
Stimulation current	0.1-2 mA (resolution: 0.1 mA), but can work accurately and be reprogrammed up to 5 mA
Pulse width	1-10 ms burst stimulation, 10-100 s "noise + DC" stimulation
Stimulation frequency	Spike frequency: 50-500 Hz, burst frequency: 1-50 Hz, noise spectrum: 0.07-100 Hz
Tone intensity	0-110 dB SPL
Tone frequency	< 8000 Hz
Stimulation duration	5½ h (from battery with capacity 800 mA/h)
Compliance voltage	19.3 V
Number of channels	3 (1 for acoustic stimulation, 2 for electrical stimulation)
User interface	Arduino IDE serial monitor
Dimensions	about 60 x 110 x 45 mm

Table 8.1: Final specifications of the multi-modal stimulator

Despite the fact that almost all the requirements have been met, the multi-modal stimulator still requires a few additional steps to be ready for the clinical tests and also some improvements may be desired to improve its functionality and performances. These are listed below:

- Building the device: PCBs, microcontroller, micro SD card module, battery (with its encase), and an on/off switch (to decouple the power supply from the rest of the circuit) have to be assembled together. Mechanical stability must be ensured as well as a proper casing. The casing must provide proper connections between the internal components and the outside to recharge the battery (in case of a rechargeable battery), connect the electrodes, connect the earbuds and connect the microcontroller to a computer;

- Miniaturization of the electronics: due to the COVID pandemic, it was not possible to get access to proper equipment or to technical aid by the university. This is the reason why the PCBs have not been realized with surface mounted components (SMDs) but with through-hole ones. As a consequence, the dimensions of the two PCBs could be drastically reduced and they could even be merged into a single one;

- Improving the noise spectrum for "noise + DC" stimulation: the "noise + DC" stimulation contains a limitation in its lower boundary. This is due to the fact that the value of the coupling capacitor in the current generator has been reduced to avoid a large size capacitor. However, SMD large value capacitors are available on the market. A correct balancing of the value of the coupling capacitor and the resistor in the high pass filter may realize the desired cut-off frequency of 0.01 Hz;

- Improving the voltage compliance: if not enough, the voltage compliance can be increased even significantly. This is possible by increasing the value of the high supply voltage generated by the boost converter. A proper selection of the resistors at the output of the MT3608 can determine an adjustment of the output voltage up to 28 V, which means that the compliance voltage can be increased to a maximum value of about 27.3 V;

- Improving the sound quality: unfortunately, the validation tests conducted are not capable of judging the quality of the sound produced by the sound generator. However, if the noise and spurious tones from the earbuds will be considered too high, there are few modifications that can reduce it. As explained in the datasheet of the LM386, bass boosting can be realized by placing a low pass filter between the specified output pins. This would also reduce the unwanted high-frequency noise experienced during the validation tests. If this is not enough, the audio amplifier can be replaced with one having better performance;

- Improving the user interface: the goal of the design of the multi-modal stimulator was to obtain an easy-to-use interface, and that has been accomplished. However, a better choice is to integrate the user interface directly in the device through for instance an LCD display. In this way, the patient could monitor the stimulation parameters and for instance the stimulation duration. Push buttons may be integrated to constantly adjust the sound volume and current amplitude. LEDs could be used to control the status of stimulation;

- Improving the volume control: the analog potentiometer can be replaced by a digital one; this would bring to a better volume adjustment. In this way, an upper limit in the volume may be introduced for people without hearing loss. Moreover, an SMD digital potentiometer would result in a much smaller total footprint.

A

Design and fabrication of the PCBs

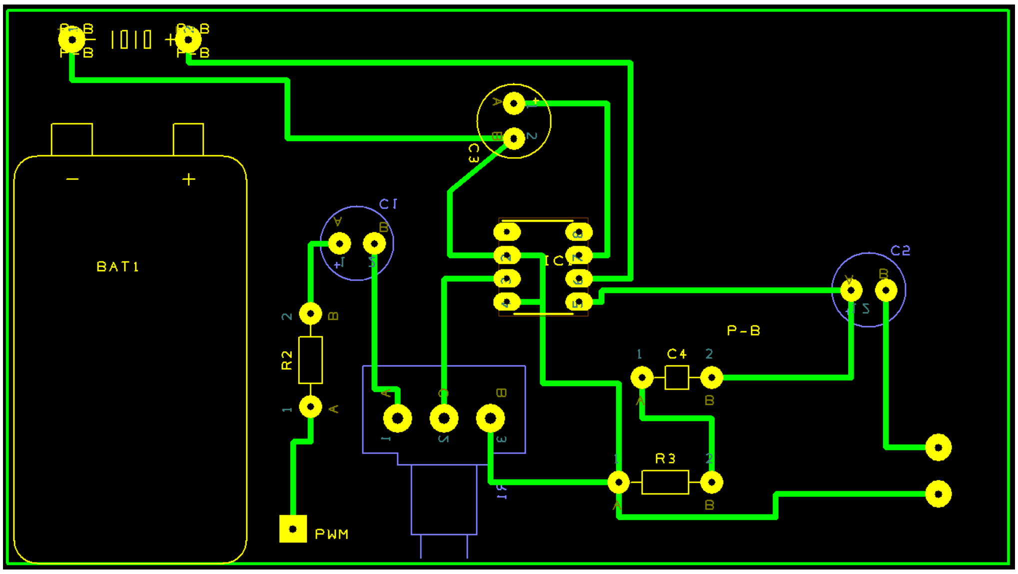


Figure A.1: PCB layout of the circuit for acoustic stimulation

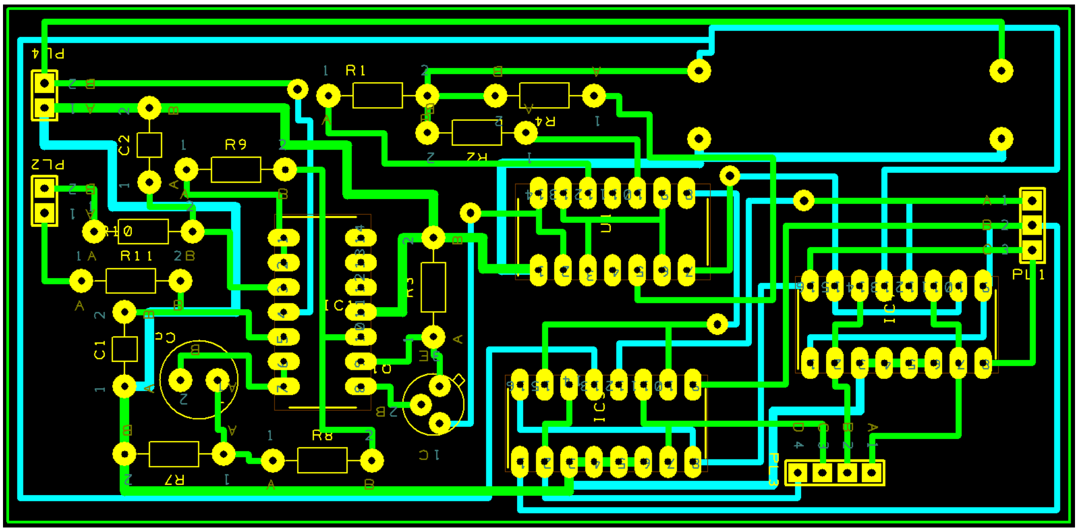


Figure A.2: PCB layout of the circuit for electrical stimulation

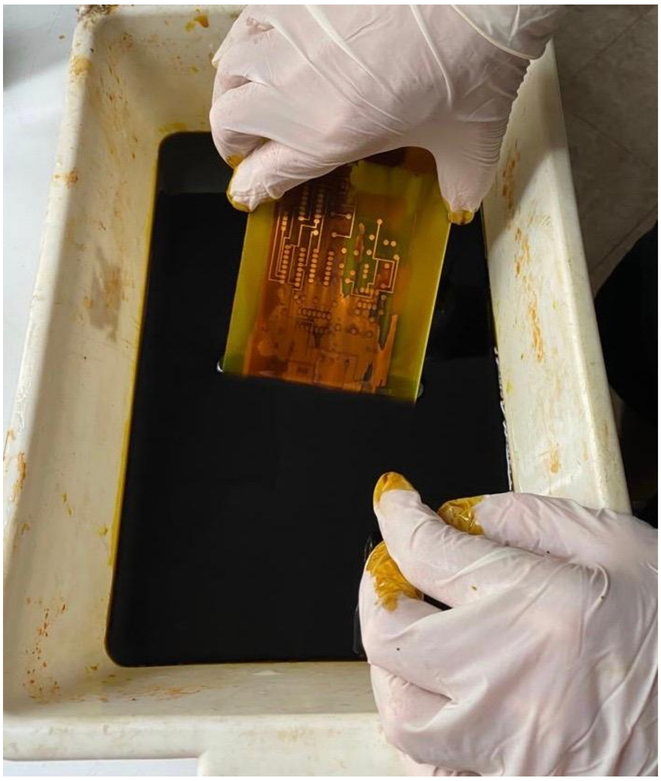


Figure A.3: Immersion of the PCB in sodium hydroxide after UV exposure

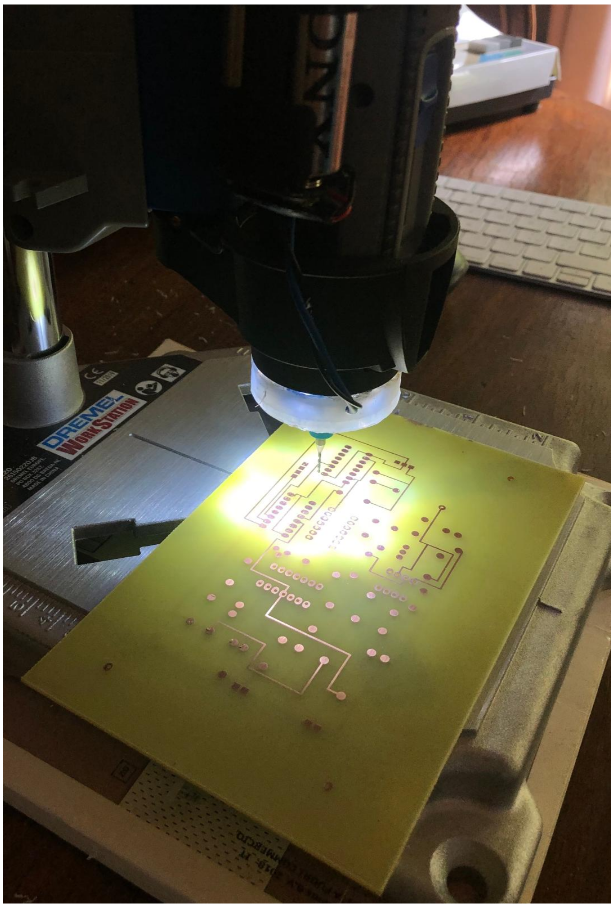


Figure A.4: PCB drilling

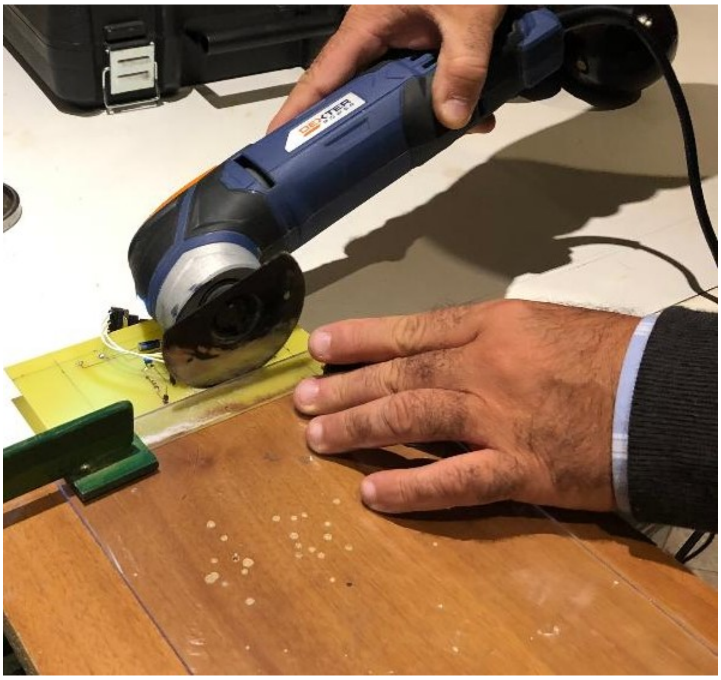


Figure A.5: PCB sawing

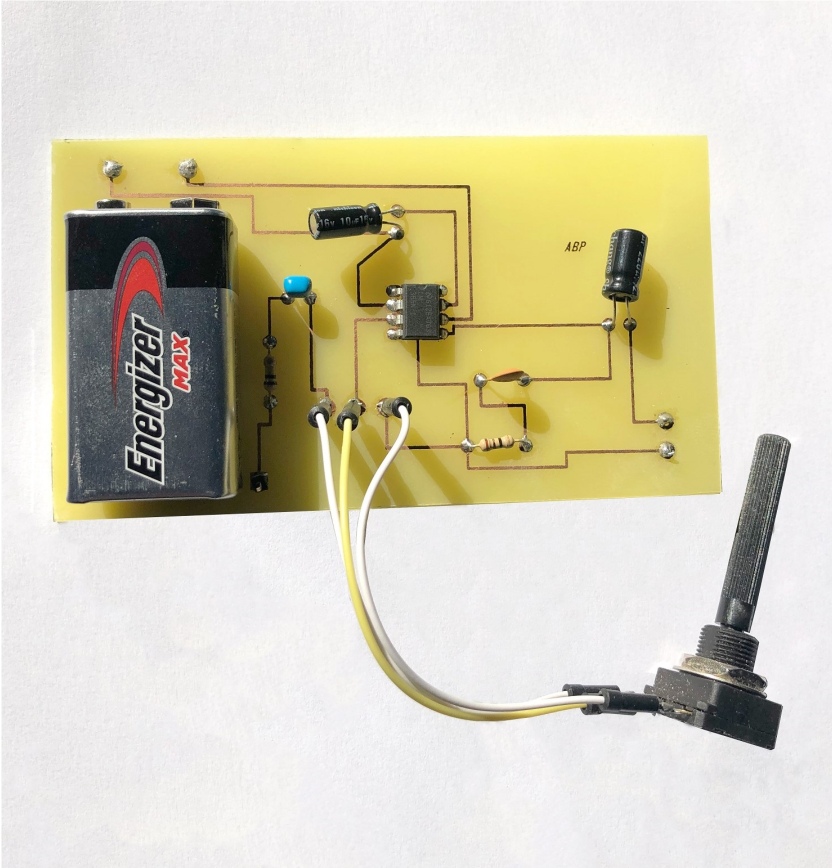


Figure A.6: Final PCB for acoustic stimulation

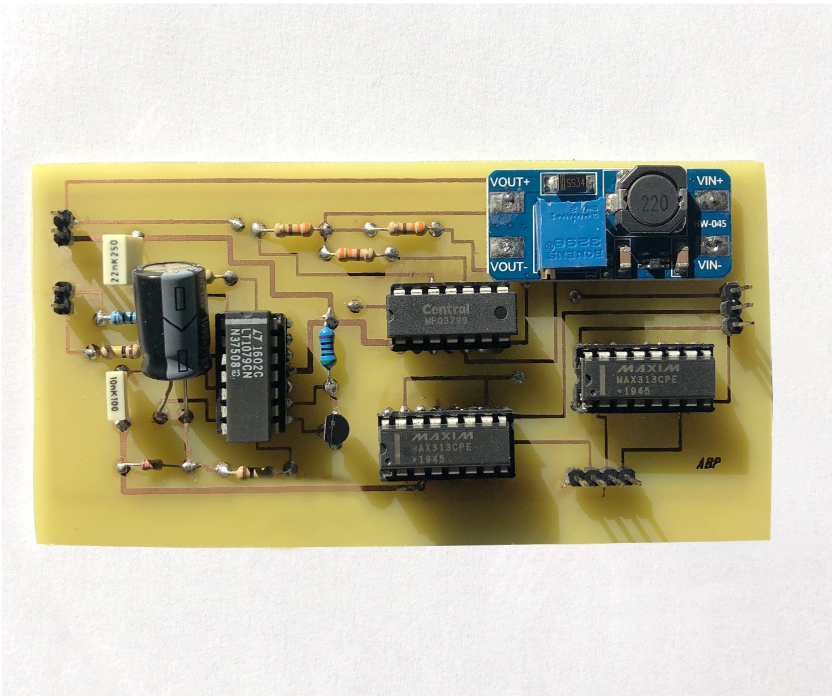


Figure A.7: Final PCB for electrical stimulation

B

Experimental setup

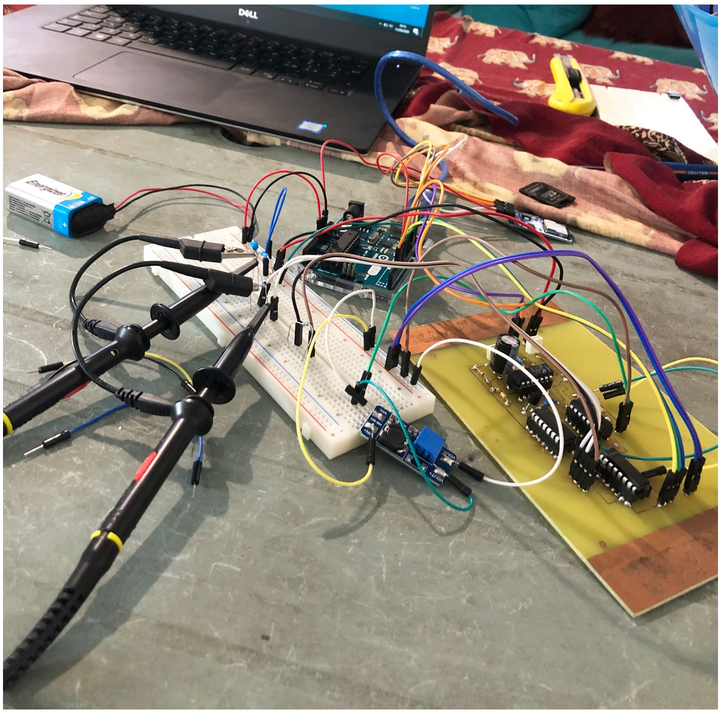


Figure B.1: Experimental setup used to test the circuit for electrical stimulation

C

Arduino programs

```
#include <pcmRF.h>
#include <TMRpcm.h>
#include <SD.h>
#include <SPI.h>

TMRpcm audio; //creation of the object audio of type TMRpcm
#define STEREO_OR_16BIT //enable stereo audio function of the library TMRpcm
#define buffSize 128 //uncomment it and the waveform may be without interrutption, then better audio
#define SD_ChipSelectPin 4
File root;

//function used to split all the input parameters (whenever a coma is found)
String getValue(String data, char separator, int index)
{
    int found = 0;
    int strIndex[] = { 0, -1 };
    int maxIndex = data.length() - 1;

    for (int i = 0; i <= maxIndex && found <= index; i++) {
        if (data.charAt(i) == separator || i == maxIndex) {
            found++;
            strIndex[0] = strIndex[1] + 1;
            strIndex[1] = (i == maxIndex) ? i+1 : i;
        }
    }
    return found > index ? data.substring(strIndex[0], strIndex[1]) : "";



}
const int tonesnumber = 100; //contains the number of tones of the audio track
const int toneduration = 1000; //contains the duration of each tone of the .WAV file (if .WAV file modified, also its value must be m
float timer = 0; //used to count when the number of bursts reach 1 second to interrupt the stimulation
float I = 0; //current amplitude
```

Figure C.1: Arduino code for intermittent acoustic and burst stimulation (1)

```
float I = 0; //current amplitude
int dutycycle = 0;
float Ws = 0; // pulse width
float Fs = 0; //spike frequency
float Fb = 0; //burst frequency
float Tb = 0; //burst period

void setup() {

TCCR2B = _BV(WGM22) | _BV(CS20); //set CS20:2 = 1, meaning a prescaler of 1
TCCR2A = _BV(WGM21) | _BV(WGM20); //set WGM22:2, WGM21:2, and WGM 20:2 = 1, meaning Fast PWM enabled with a max value set by the r
OCR2A = 100; //setting MAX level to 100 (from original 255), meaning a PWM frequency of around 150 kHz

pinMode(6,OUTPUT);
pinMode(7,OUTPUT);
pinMode(8,OUTPUT);
pinMode(3,OUTPUT); //setting output for DC/Burst stimulation (the second output will be either pin 9 or 10)


Serial.begin(115200);
Serial.println("Insert values for current amplitude [mA], spike frequency [Hz], burst frequency [Hz] (separated by a coma): ");

while(Serial.available() ==0){}
  String s = Serial.readString();
  float current = getValue(s,',',0).toFloat();
  float spikefreq = getValue(s,',',1).toFloat();
  float burstfreq = getValue(s,',',2).toFloat();
  if (current < 0 || current > 2 || spikefreq < 50 || spikefreq > 500 || burstfreq < 1 || burstfreq > 50){
    Serial.println("Input not valid");
    }
  else {
    I = current;
    dutycycle = (100*I)/5;
    Fs = spikefreq;
```

Figure C.2: Arduino code for intermittent acoustic and burst stimulation (2)

```
    Tb = (1/Fb)*1000; //burst period

  }
  //print all the input parameters
  Serial.println(I);
  Serial.println(Ws);
  Serial.println(Fs);
  Serial.println(Fb);
  Serial.println(Tb);



if (!SD.begin(SD_ChipSelectPin)) {
    Serial.println("failed!");
    while(true);  // stay here.
  }
Serial.println("OK!");
audio.speakerPin = 9;  // set speaker output to pin 9
pinMode(10,OUTPUT);

root = SD.open("/");      // open SD card main root

audio.setVolume(5);    //   0 to 7. Set volume level //in term of time signal, it alters the offset: higher volume means highe
audio.quality(1); //Set 1 for 2x oversampling Set 0 for normal

}


void loop() {
  // put your main code here, to run repeatedly:

//for burst stimulation the PIN9 must be zero  whcih is the output that goes to the summation amplifier
audio.play("Noise.wav");
```

Figure C.3: Arduino code for intermittent acoustic and burst stimulation (3)

```
digitalWrite(8,HIGH);
//repetition of the same pattern till the end of the sound, which should be made of 100 tones
for (int j = 0; j<tonesnumber; j++){
 analogWrite(9,0);
 //repetion of burst until the timer does not reach 1 second, when the stimulation must be interrupted for 1 second
 while(timer < toneduration){

 analogWrite(3,dutycycle);
 //single burst generation
 for (int i =1; i<6; i++){
  digitalWrite(6,HIGH);
  digitalWrite(7,LOW);
  delay(Ws);
  digitalWrite(7,HIGH);
  delay(Ws);
 }
 digitalWrite(6,LOW);
 digitalWrite(7,HIGH);
 delay(5*Ws);
 //analogWrite(3,0);
 digitalWrite(6,HIGH);
 digitalWrite(7,HIGH);

 delay(Tb-(15*Ws)); //it is the interburst delay
 timer = timer + Tb;
}
 digitalWrite(6,HIGH);
 digitalWrite(7,HIGH);
//analogWrite(3,0);
//analogWrite(10,0);
delay(toneduration); //no stimulation for the time specified by the tone duration
timer = 0;
}
```

Figure C.4: Arduino code for intermittent acoustic and burst stimulation (4)

```
#include <pcmRF.h>
#include <TMRpcm.h>
#include <SD.h>
#include <SPI.h>

TMRpcm audio; //creation of the object audio of type TMRpcm
#define STEREO_OR_16BIT
#define buffSize 128 //uncomment it and the waveform may be without interrutption, then better audio
#define SD_ChipSelectPin 4
File root;

String getValue(String data, char separator, int index)
{
    int found = 0;
    int strIndex[] = { 0, -1 };
    int maxIndex = data.length() - 1;

    for (int i = 0; i <= maxIndex && found <= index; i++) {
        if (data.charAt(i) == separator || i == maxIndex) {
            found++;
            strIndex[0] = strIndex[1] + 1;
            strIndex[1] = (i == maxIndex) ? i+1 : i;
        }
    }
    return found > index ? data.substring(strIndex[0], strIndex[1]) : "";

}

const int songduration = 200000; //contains the duration of the audio track used for acoustic stimulation
float timer = 0; //used to count when the number of bursts reach 1 second to interrupt the stimulation
float DC = 0; //current amplitude
int dutycycle = 0;
float duration = 0; // duration of each stimulation phase
```

Figure C.5: Arduino code for intermittent acoustic stimulation and non-intermittent "noise + DC" stimulation (1)

```
void setup() {

TCCR2B = _BV(WGM22) | _BV(CS20); //set CS20:2 = 1, meaning a prescaler of 1
TCCR2A = _BV(WGM21) | _BV(WGM20); //set WGM22:2, WGM21:2, and WGM 20:2 = 1, meaning Fast PWM enabled with a max value set by the regis
OCR2A = 100; //setting MAX level to 100 (from original 255), meaning a PWM frequency of around 150 kHz

pinMode(6,OUTPUT);
pinMode(7,OUTPUT);
pinMode(8,OUTPUT);
pinMode(3,OUTPUT); //setting output for DC/Burst stimulation (the second output will be either pin 9 or 10)


  // put your setup code here, to run once:
Serial.begin(115200);
Serial.println("Insert values for DC amplitude [mA] and phase duration [s] (separated by a coma): ");

while(Serial.available() ==0){}
  String s = Serial.readString();
  float current = getValue(s,',',0).toFloat();
  float dur = getValue(s,',',1).toFloat(); //in seconds
  Serial.println(current);
  Serial.println(dur);
  if (current < 0 || current > 2 || dur < 10 || dur > 100){
    Serial.println("Input not valid");
    }
  else {
    DC = current;
    dutycycle = (100*DC)/5;
    duration = dur*1000;

  }
```

Figure C.6: Arduino code for intermittent acoustic stimulation and non-intermittent "noise + DC" stimulation (2)

```
  Serial.println(DC);
  Serial.println(duration);

if (!SD.begin(SD_ChipSelectPin)) {
    Serial.println("failed!");
    while(true);  // stay here.
  }
Serial.println("OK!");
audio.speakerPin = 9;  // set speaker output to pin 9
pinMode(10,OUTPUT);    //set speaker output to pin 10

root = SD.open("/");      // open SD card main root

audio.setVolume(5);    //   0 to 7. Set volume level //in term of time signal, it alters the offset: higher volume means hi
audio.quality(1); //Set 1 for 2x oversampling Set 0 for normal

}

void loop() {
  // put your main code here, to run repeatedly:

//for burst stimulation the PIN9 must be zero  whcih is the output that goes to the summation amplifier
audio.play("Noise.wav");
```

Figure C.7: Arduino code for intermittent acoustic stimulation and non-intermittent "noise + DC" stimulation (3)

```
//timer is used to determine how many times the noise period has to be repetead before the beginning of the song: if the son
//the electrical stimulation must repeat until timer equal 100 seconds
while(timer <= songduration){
digitalWrite(8,HIGH);

analogWrite(3,dutycycle);
digitalWrite(6,HIGH);
digitalWrite(7,LOW);
delay(duration);
digitalWrite(6,LOW);
digitalWrite(7,HIGH);
delay(duration);
timer = timer + 2*duration;

}

}
```

Figure C.8: Arduino code for intermittent acoustic stimulation and non-intermittent "noise + DC" stimulation (4)

D

Boost converter module

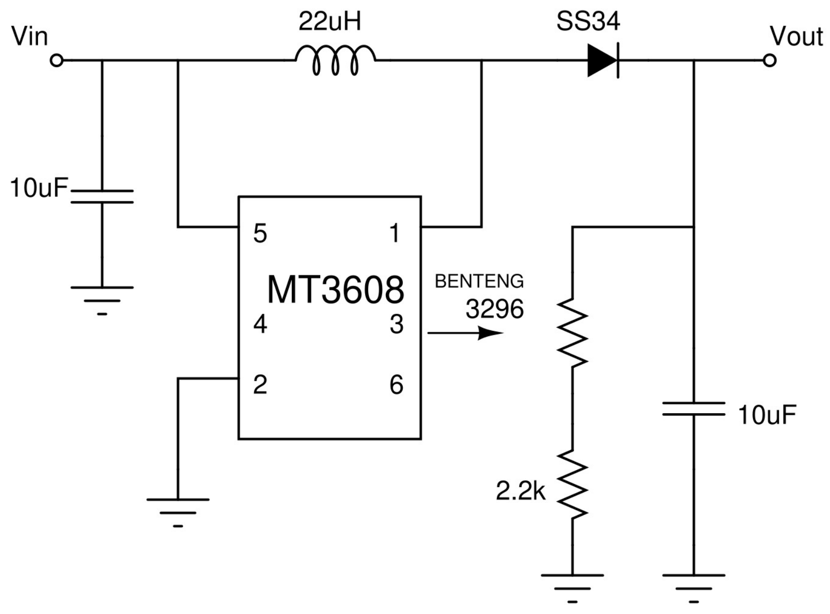


Figure D.1: Circuit of the MT3608 boost converter module

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