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Designing Accessible Hardware for Electrical Neuromodulation Applications

Konstantina Kolovou Kouri



DESIGNING ACCESSIBLE HARDWARE FOR ELECTRICAL NEUROMODULATION APPLICATIONS

TO ENHANCE STIMULATION SAFETY, SELECTIVITY AND
POWER EFFICIENCY

DESIGNING ACCESSIBLE HARDWARE FOR ELECTRICAL NEUROMODULATION APPLICATIONS

**TO ENHANCE STIMULATION SAFETY, SELECTIVITY AND
POWER EFFICIENCY**

Dissertation

for the purpose of obtaining the degree of doctor
at Delft University of Technology
by the authority of the Rector Magnificus, Prof. dr. ir. H. Bijl,
Chair of the Board for Doctorates
to be defended publicly on
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by

Konstantina KOLOVOU KOURI

This dissertation has been approved by the promotor.

Composition of the doctoral committee:

Rector Magnificus	Chairperson
Prof. dr. ir. W.A. Serdijn	Delft University of Technology, <i>promotor</i>
Dr. V. Giagka	Delft University of Technology, <i>promotor</i>

Independent members:

Prof. dr. P.J. French	Delft University of Technology
Prof. dr. E.C.T. van der Helm	Delft University of Technology
Prof. dr.-Ing. K. Seidl	University of Duisburg-Essen, Germany
Prof. dr. S. Raspopovic	Medical University of Vienna, Austria
Dr. V. Valente	Toronto Metropolitan University, Canada



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*To Bertrand.
Who deserves an honorary PhD.*

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SUMMARY

From the development of the first cochlear implant in 1957 until this day, neural implants have been successfully treating neurological diseases and disorders by directly interfacing with the biological tissue. Electrical stimulation, the most common form of neuromodulation, can excite or inhibit the activity of neural cells, thus inducing targeted therapeutic effects and alleviating symptoms, or restoring lost or degenerating functions of the nervous system. The development of implantable devices has seen great progress over the past decades, improving their functionality, robustness and lifetime. Still, many key features of commercial devices remain unchanged, given their technological maturity and the demanding and complex procedures required for their medical use approval. However, the constant advancement of technology and neuroscientific knowledge calls for further improvement and development of the functionality and configuration of neural implants. To this end, this thesis explores means of enhancing the capabilities of implantable devices through a higher programmability of the stimulation parameters, the integration of wireless powering, and the introduction of methods to increase energy efficiency and stimulation efficacy. Two neural stimulators are designed and developed, one for the purpose of dorsal root ganglion (DRG) stimulation for motor recovery after a spinal cord injury, and one designed for, but not limited to, vagus nerve stimulation applications. They are developed as benchtop prototypes, using commercially available components to increase their accessibility and reproducibility by other research labs, and are intended for experimental preclinical and clinical studies. The safety of the devices is considered a high priority, by taking the necessary measures to provide a safe operation, such as developing and integrating mechanisms that monitor and compensate for unwanted reactions at the targeted tissue site. Both designs offer multichannel operation for increased stimulation specificity and spatial resolution by individually controlling the electrodes connected to the system's output. Following the emerging trends in the design of neural implants, and working towards miniaturised and low-power systems, various methods for improving power efficiency are explored and implemented. An adaptive power supply architecture is proposed to increase energy efficiency in systems that perform non-rectangular waveform stimulation. Furthermore, the possibility of entirely eliminating the need for a constant power supply is investigated and implemented, increasing the system's energy efficiency by wirelessly powering the device through ultrasound while using the same transferred and rectified signal for both powering and neural stimulation. The development of such hardware aims at enhancing neuroscientific knowledge by providing advanced, functional solutions that follow current needs and requirements, and can aid in further exploring the potential of neuromodulation applications in providing targeted, personalised therapies.

SAMENVATTING

Vanaf de ontwikkeling van de eerste cochleaire implantaat in 1957 tot op de dag van vandaag hebben neurale implantaten met succes neurologische ziekten en aandoeningen behandeld door een directe interactie met het biologische weefsel. Elektrische stimulatie, de meest voorkomende vorm van neuromodulatie, kan de activiteit van neurale cellen opwekken of afremmen en zo gerichte therapeutische effecten teweegbrengen en symptomen verlichten, of verloren of degenererende functies van het zenuwstelsel herstellen. De ontwikkeling van implanteerbare apparaten heeft de afgelopen decennia grote vooruitgang geboekt, waardoor hun functionaliteit, robuustheid en levensduur zijn verbeterd. Toch blijven veel belangrijke kenmerken van commerciële hulpmiddelen onveranderd, gezien hun technologische rijpheid en de veeleisende en complexe procedures die vereist zijn voor goedkeuring voor medisch gebruik. De voortdurende vooruitgang van technologie en neurowetenschappelijke kennis vraagt echter om verdere verbetering en ontwikkeling van de functionaliteit en configuratie van neurale implantaten. Daarom worden in dit proefschrift middelen onderzocht om de mogelijkheden van implanteerbare apparaten te verbeteren door een grotere programmeerbaarheid van de stimulatieparameters, de integratie van draadloze voeding en de introductie van methoden om de energie-efficiëntie en de doelmatigheid van de stimulatie te verhogen. Er worden twee neurale stimulators ontworpen en ontwikkeld, één voor het doel van stimulatie van het dorsaal wortelganglion (DRG) voor motorisch herstel na een dwarslaesie, en één ontworpen voor, maar niet beperkt tot, toepassingen voor stimulatie van de nervus vagus. Ze worden ontwikkeld als laboratoriumprototypes, waarbij commercieel verkrijgbare componenten worden gebruikt om de toegankelijkheid en reproduceerbaarheid voor andere onderzoekslaboratoria te vergroten, en zijn bedoeld voor preklinische en klinische studies. De veiligheid van de apparaten heeft een hoge prioriteit, waarbij de nodige maatregelen worden genomen voor een veilige werking, zoals het ontwikkelen en integreren van mechanismen die ongewenste reacties op de plaats van het doelweefsel controleren en compenseren. Beide ontwerpen bieden meerkanaals werking voor meer stimulatiespecificiteit en ruimtelijke resolutie door de elektroden die zijn aangesloten op de uitgang van het systeem individueel te regelen. Naar aanleiding van de opkomende trends in het ontwerp van neurale implantaten en het toewerken naar geminiaturiseerde en energiezuinige systemen, worden verschillende methoden voor het verbeteren van de energie-efficiëntie onderzocht en geïmplementeerd. Er wordt een adaptieve voedingsarchitectuur voorgesteld om de energie-efficiëntie te verhogen in systemen die niet-rechthoekige golfvormstimulatie uitvoeren. Verder wordt de mogelijkheid onderzocht en geïmplementeerd om de noodzaak van een constante voeding volledig te elimineren, waardoor de energie-efficiëntie van het systeem wordt verhoogd door het apparaat draadloos te voeden via ultrageluid, terwijl hetzelfde overgedragen en gelijkgerichte signaal wordt gebruikt voor zowel de energievoorziening als neurale

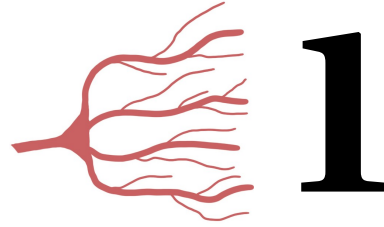
stimulatie. De ontwikkeling van dergelijke hardware is gericht op het verbeteren van de neurowetenschappelijke kennis door geavanceerde, functionele oplossingen te bieden die voldoen aan de huidige behoeften en vereisten, en kan helpen bij het verder onderzoeken van het potentieel van neuromodulatietoepassingen voor het bieden van gerichte, gepersonaliseerde therapieën.

ACRONYMS

ADC	analog-to-digital converter
Ag/AgCl	silver/silver chloride
AP	action potentials
ASIC	application specific integrated circuit
CB	charge balancing
CCS	constant current stimulation
CMS	current mode stimulation
DBS	deep brain stimulation
DC	direct current
DDC	DC/DC converter
DI	deionised
DRG	dorsal root ganglion
DT	dead time
eCAPs	evoked compound action potentials
EEG	electroencephalogram
EIS	electrochemical impedance spectroscopy
EMG	electromyography
EPG	external pulse generator
eSCS	epidural spinal cord stimulation
ETI	electrode-tissue interface
FSM	finite state machine
GBW	gain bandwidth

GUI		graphical user interface
HCS		howland current source
HPF		high-pass filter
HV		high-voltage
IC		integrated circuit
IMDD		Investigational Medical Device Dossier
IPG		implantable pulse generator
ISR		interrupt service routine
KHFAC		kilohertz frequency alternating current
LDO		low-dropout
LPF		low-pass filter
MCU		microcontroller unit
MOPP		Means Of Patient Protection
MRI		magnetic resonance imaging
MUX		multiplexer
NC		normally closed
NFC		near-field communication
OC		offset compensation
OpAmp		operational amplifier
PBS		phosphate-buffered saline
PID		proportional-integral-derivative
PNS		peripheral nerve stimulation
PRR		pulse repetition rate
Pt		platinum
PtIr		platinum-iridium

PV		process variable
PWM		pulse width modulation
RF		radio frequency
RX		receiver
SARs		specific absorption rates
SC		spinal cord
SCI		spinal cord injury
SP		set-point
SPST		single-pole, single-throw
SR		slew rate
TX		transmitter
UHFPS		ultra-high frequency pulsed stimuli
US		ultrasound
VCCS		voltage-controlled current source
VL		vastus lateralis
VMS		voltage mode stimulation
VNS		vagus nerve stimulation
WPT		wireless power transfer
μC		microcontroller



INTRODUCTION

*I'm not interested in my lab engaging in matters that are just interesting,
but in technology that is useful to people.
(personal translation)*

Michael Dertouzos

1.1. RESEARCH OBJECTIVE: DESIGNING BIOELECTRONIC HARDWARE TO BE USED IN EXPERIMENTAL SETTINGS

To this day, a great number of patients have benefited from the therapeutic potential that neural implants have to offer. The use of implantable electronics that interface with biological tissue, also known as bioelectronics, can alleviate symptoms in diseases and disorders like Parkinson's or essential tremors [1], restore lost or degenerating functions of the nervous system in cases of a spinal cord injury, visual or hearing impairment [2–4], as well as manage neuropathic pain [5]. Unlike the administration of pharmacological agents as a means of treatment, the typical and conventional way of treating such disorders, bioelectronics promise reduced side effects and improved efficiency during a personalised therapy. By directly interacting with the central and peripheral nervous systems, bioelectronic implants can modulate the activity of nerve cells in a targeted manner.

From the development of the first cochlear implant in 1957 [6] to the 2017 FDA approval of vagus nerve stimulation (VNS) therapy for epilepsy in children as young as 4 years old [7], neural implants have demonstrated great progress. Nevertheless, some of the main characteristics of the devices that are available for therapy to the public remain generally unchanged, due to their advanced technological maturity and the complex and rigorous procedures from the device development until its medical use approval. The most established form of neuromodulation has been and still is electrical stimulation, given its wide applicability and efficacy, at times in combination with pharmacological drug administration [8]. Most commercially available implants have a bulky form factor and are enclosed in a rigid, hermetically sealed casing [8, 9]. They are powered through batteries and, if not rechargeable, their limited lifetime requires them to be exchanged during surgery, introducing additional procedural risks.

The ongoing therapeutic success of bioelectronics has led to their consistent development, in order to continuously improve their therapeutic benefits while trying to advance current neuroscientific research [10]. This essentially requires constant technological progress in order to cover the rising and progressively identified needs. Such requirements include the improvement of the device's durability and power efficiency, its functionality and overall capabilities.

In recent years, a number of different modalities have emerged as successful potential candidates for stimulating the nerves, such as optical or acoustic neuromodulation [10, 11]. Both methods are emerging and still being explored; however, they show good prospects in achieving higher spatial resolution and increasing selectivity. Furthermore, current research explores the exploitation of multiple stimulation modalities, by combining electrical, pharmacological, optical and acoustic stimulation [8]. Commonly known as multimodal operation, this can enhance the level of spatiotemporal control and increase the stimulation specificity and safety [8].

Spatial precision and selectivity heavily influence the success of therapeutic outcomes. However, therapies often need to be monitored and administered or adjusted as needed. To this end, replacing passive probes with active

ones while introducing physiological recording leads to an optimised closed-loop neuromodulation, based on the response of the recorded neuronal activity [8, 9]. Furthermore, the electrode count, configuration and placement can achieve precise and selective stimulation by appropriately manipulating the electric field around the targeted stimulation area [11].

Moving towards miniaturised, sustainable neural implants, large, bulky batteries need to be replaced by lightweight rechargeable batteries or simple storage elements. By introducing wireless power transfer (WPT) techniques for powering implantable devices, the need for battery replacement can be circumvented. Some of the most commonly used techniques include far-field (RF antennas) and near-field (inductive coupling between two coils) electromagnetic waves, photovoltaic technologies and acoustic waves (ultrasound) [8, 12]. Depending on the application, all techniques come with certain advantages and disadvantages regarding their maximum available power yield, implantation depth for adequate power transfer and miniaturisation potential.

Addressing the emerging trends in the functionality and design of neural implants requires the upgrade of existing hardware. This thesis tackles this demand by providing accessible and low-cost designs that leverage existing, well-established solutions and use commercially available components to serve the needs of various neuromodulation applications. The implemented designs deliberately prioritise accessibility, reproducibility, and modularity, thus adopting an open-hardware-oriented design philosophy. This approach enables independent system implementation and validation by different research labs, in contrast to many reported systems that remain difficult to reproduce outside the originating group due to the use of custom integrated circuits or specialised fabrication processes, and aims to promote cumulative scientific progress in the field.

To this extent, two neural stimulators were designed and developed, each specialising in a different neuromodulation application, with features that serve the individual applications' needs. In both cases, by providing the possibility for multichannel stimulation, the developed electronic hardware can address issues such as multisite access, increased spatial resolution and increased stimulation specificity. This is achieved by interfacing with and independently controlling a large number of stimulation electrodes. While working towards miniaturised and low-power systems, with a focus on electrical stimulation, different means of enhancing power efficiency are investigated and implemented. This includes the appropriate choice of low-power components, as well as the proposal and integration of energy-efficient architectures. In this regard, an adaptive power supply is proposed as a means of increasing energy efficiency in systems that perform arbitrary waveform stimulation. Furthermore, the potential of entirely eliminating the need for a constant power source is explored, while realising wireless power transfer through ultrasound and using the harvested signal for powering the device, but also for neural stimulation. Throughout every design process, safety aspects, given the direct contact with the neural tissue, remain a high priority. This extends from the safety of the device as a whole to the safety of electrically stimulating neural tissue and the effects this can have on both the tissue and the interfacing electrodes. Such novel hardware

can aid in enhancing neuroscientific knowledge by further exploring the potential of bioelectronics, while providing elegant solutions for advanced neuromodulation hardware design challenges.

1.2. OUTLINE OF THE THESIS

The remainder of this thesis is organised as follows:

Chapter 2: Design Considerations for Electrical Neuromodulation Systems

This chapter provides an overview of the main building blocks and components of state-of-the-art electrical neuromodulation systems through a literature review. It goes over the fundamental mechanisms that allow for the electrical stimulation of neural tissue through the generation and propagation of action potentials, and differentiates between the possibility of exciting vs. inhibiting the activity of nerve cells. Furthermore, it highlights the importance of safety during stimulation when designing neurostimulators, describes the processes that can lead to unwanted charge accumulation at the electrode-tissue interface and thus to damage of the neural interface and the surrounding tissue, and identifies techniques that can aid in minimising these harmful effects. With recent designs moving towards battery-less systems and systems with rechargeable batteries, different wireless power transfer modalities are reviewed, focusing on the use of ultrasound as a means of transferring power. Finally, some of the mechanisms that can increase power efficiency and stimulation efficacy are introduced, and state-of-the-art neuromodulation systems that follow current advancements in the field are identified.

Chapter 3: Designing Neuromodulation Hardware for a Clinical Setting

Designing neuromodulation hardware with the aim of using it in preclinical or clinical settings requires a design that is user-friendly, accommodates the needs for the intended application and, very importantly, is safe. Chapter 3 presents the process of addressing these requirements through the design and development of a dorsal root ganglion (DRG) stimulator system intended for use in early clinical trials for motor recovery after spinal cord injury (SCI). The system is built entirely using commercially available components and allows for independent control of multilevel bilateral stimulation. Attempting to increase the patient safety of this and similar neurostimulator devices given the direct contact with neural tissue, a broad frequency range charge balancing system was designed to be used as an add-on system for neural stimulators. While continuously monitoring the offset voltage buildup at the electrode site, it applies a corrective current to the electrode to compensate for the charge accumulation that leads to this voltage buildup.

Chapter 4: Ultrasonically Powered Neuromodulation Platform Intended for Spatially and Directionally Selective Electrical Stimulation

Among the well-established applications of electrical neuromodulation, VNS has proven to be an effective means of treating disorders such as epilepsy and depression. To explore the potential that recent neuroscientific advancements have

identified in VNS, an ultrasonically powered neuromodulation platform has been developed as a practical and versatile experimental tool, using only off-the-shelf components for ease of reproducibility by other research labs. The platform can perform both neural activity excitation and inhibition, allowing further exploration of spatially and directionally selective stimulation, using voltage-controlled biphasic and monophasic stimulation pulses. It supports a connection to 6 electrodes for excitation and 2 for inhibition, and includes a charge balancing mechanism based on a digital proportional-integral-derivative (PID) controller to enhance stimulation safety. To increase energy efficiency, the same signal used for powering the platform is utilised for neural stimulation, eliminating the need for an additional voltage or current source. This chapter describes the design and development process of the neuromodulation platform, characterises its key components and validates its functionality within a lab experimental setup.

Chapter 5: On the Efficiency and Efficacy of Stimulating with Non-Rectangular Pulses

Working towards the miniaturisation of neurostimulators and the development of battery-less, wirelessly-powered systems, it is essential to explore means of increasing their energy efficiency and stimulation efficacy. This chapter highlights the energy savings that an adaptive supply can achieve for a system that offers programmable non-rectangular stimulation pulses. Through a system-level analysis carried out in Matlab, the possible energy savings of the proposed adaptive supply with 6 supply levels are calculated and compared to the conventional approach with a fixed supply.

Chapter 6: Conclusion & Recommendations for Future Work

This chapter presents the conclusions of this thesis, highlights its contributions and provides recommendations for future work.

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DESIGN CONSIDERATIONS FOR ELECTRICAL NEUROMODULATION SYSTEMS

*What you do makes a difference,
and you have to decide what kind of difference you want to make.*

Jane Goodall

2.1. MODULATION OF NEURAL ACTIVITY

2.1.1. FUNDAMENTALS OF NEURAL STIMULATION

2

The most common form of neural stimulation, electrical stimulation, involves delivering signals, usually in the form of electrical currents or voltages, from a neural stimulator to the tissue via a conductive electrode. The electrical stimulation of neural tissue has been for many decades an established technique for treating diseases and disorders that result from an impaired function of the nervous system by targeting various nerves in the human body [1]. The electrical stimulation of nerve cells is possible since neurons rely on electrical signals for communication, a process made possible through the generation and propagation of action potentials (AP). Fig. 2.1 illustrates the process of an AP generation that occurs after a stimulus triggers the firing of a nerve cell.

At the core of this mechanism lies the neuron's resting membrane potential, typically maintained at approximately -60 to -80 mV [2] (Fig. 2.1, Phase 1). This potential is established across the lipid bilayer of the neuron's membrane, which separates the intracellular and extracellular environments. Embedded within this bilayer are voltage-gated ion channels, mainly sodium (Na^+) and potassium (K^+) ones, which play a crucial role in maintaining and altering the membrane potential [2, 3]. When the membrane potential is depolarised and exceeds a specific threshold (around -55 mV) (Fig. 2.1, Phase 2), voltage-gated sodium channels open, allowing Na^+ ions to flow into the nerve cell. This influx of positive ions leads to the full depolarisation of the neuron's membrane and initiates an AP (Fig. 2.1, Phase 3), causing the membrane potential to rise to nearly $+30$ to 40 mV [2, 3]. The depolarisation phase is followed by repolarisation (Fig. 2.1, Phase 4), where the activity of the sodium channels decreases, while the potassium channels open, allowing K^+ ions to exit the cell and thus restoring the negative internal environment of the cell [2, 3]. After repolarisation and during the hyperpolarisation phase, the membrane potential overshoots in the negative direction and goes below the resting membrane potential (Fig. 2.1, Phase 5) [2, 3]. In the final stage of this mechanism, the resting membrane potential is re-established (Fig. 2.1, Phase 6).

APs can propagate along the nerve and do not change their strength over the distance they travel. The triggering of an AP in one part of the neuron can trigger the same response in a neighbouring part, resulting in a chain reaction and a wave-like propagation of the electrical signal along the neuron [3]. To extend the communication between multiple neurons, another mechanism is involved. Between neurons, the communication occurs at the so-called synapses. There, a chemical, namely a neurotransmitter, is released, and crossing the synaptic cleft, it binds to specific receptors of neighbouring neurons [5, 6]. This communication through electrical and chemical signals allows for the efficient and quick transmission of information over long distances within the nervous system.

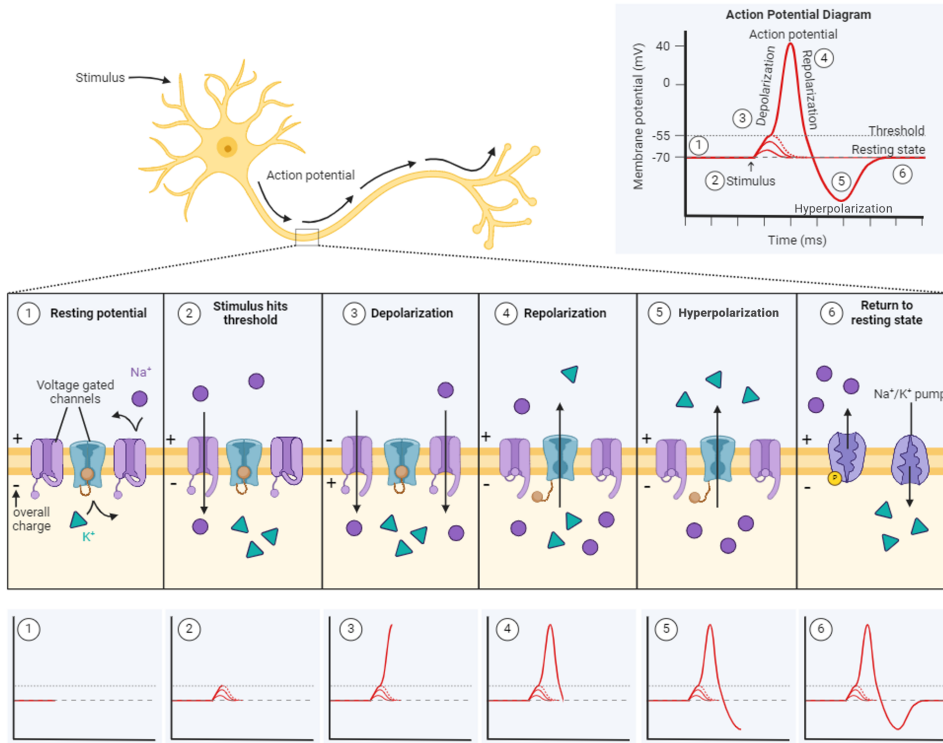


Figure 2.1: Process of action potential AP generation after being elicited by an electrical stimulus. As soon as the cell membrane potential crosses a specific threshold, it depolarises, altering the internal cell potential. The depolarisation phase is followed by repolarisation and hyperpolarisation, after which the resting membrane potential is re-established. Figure adapted with BioRender from [4].

2.1.2. EXCITATION VS. INHIBITION OF NEURAL ACTIVITY

While applying an electrical stimulus with the purpose of eliciting and propagating an AP can activate a neuron, an electrical stimulus can also be applied to inactivate it. Neural activity can either be evoked (causing APs to be generated and propagate) or suppressed (blocking APs from propagating), depending on the pulse repetition rate (PRR), waveform and amplitude of the applied stimulation pattern. The two most common methods for achieving nerve conduction block are direct current (DC) stimulation and kilohertz frequency alternating current (KHFAC) stimulation [7]. While neural excitation typically uses frequencies below 500 Hz, KHFAC works in the kilohertz domain, certainly above 1 kHz, mainly above 5 kHz [8]. Fig. 2.2 illustrates the waveforms and PRRs typically used for neural activity excitation and inhibition. Though both methods have been successful in blocking nerve activity, KHFAC is preferred over DC block, as in the case of the latter technique, the constant application of direct current to the tissue eventually results in damage to both the

tissue and the electrode [9].

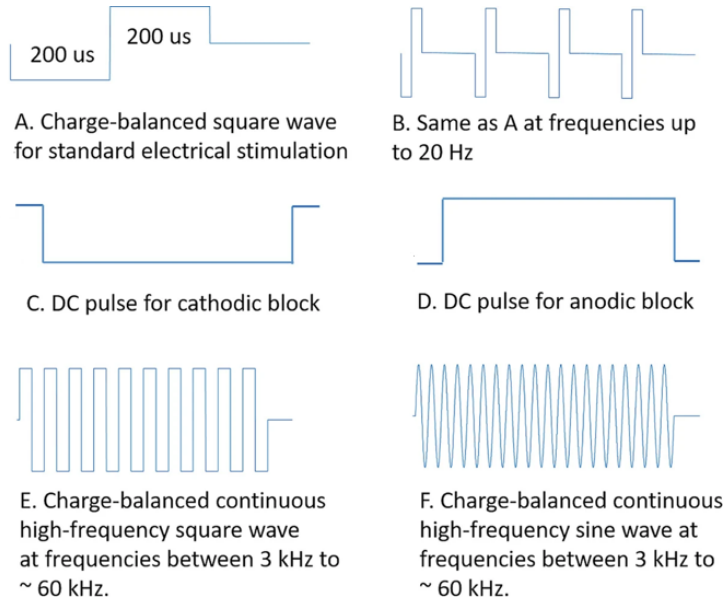


Figure 2.2: Waveforms and pulse repetition rates typically used for nerve activation (A and B) and blocking (C and D - DC block, E and F - KHFAC block). Figure adapted from [7].

There are two mechanisms that have been identified as leading to a successful conduction block when applying KHFAC stimulation [10]. First, conduction block can be the result of synaptic fatigue since the successive high-frequency pulses applied to the nerve can deplete the available neurotransmitters. Second, KHFAC stimulation can directly block the ability of the nerve to conduct APs, by locally blocking their transmission at the site of the blocking electrode [8, 11].

Electrical nerve block offers a reliable means of blocking nerve activity, having a quick onset (as quickly as 5 and 10 ms [12]) while being fully and rapidly reversible within a few hundred milliseconds [9, 13], as can be seen on Fig. 2.3. One identified drawback that results from the use of KHFAC blocking is the “onset response” [10, 13]. This refers to a brief increase of nerve activity at the start of the KHFAC block. Attempts to mitigate this effect include the alteration of the stimulation electrode geometry, the manipulation of the frequency-amplitude responses of the KHFAC block and the combination of DC with the KHFAC stimulation [7].

2.2. STIMULATION SAFETY

2.2.1. STIMULATION PULSE & NEED FOR CHARGE BALANCING

Using electrical signals to modulate neural activity is possible through a conductive electrode providing the interface to the neural tissue and allowing for the necessary

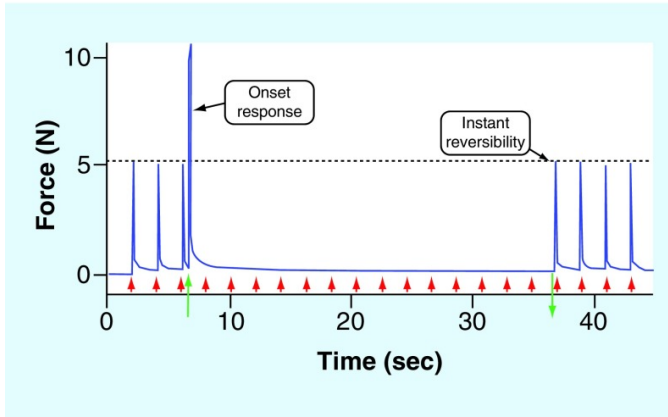


Figure 2.3: Demonstration of KHFAC block delivery and the resulting onset response and subsequent seizing of nerve activity. The KHFAC delivery starts at 7 s (green arrow pointing up) and is stopped 30 s later (green arrow pointing down). An initial onset response is visible when the KHFAC commences. Figure taken from [9], © 2017, reprinted by permission of Informa UK Limited, trading as Taylor & Francis Group, <https://www.tandfonline.com>.

charge displacement to trigger neural activation. Although a monophasic stimulation pulse suffices to elicit activation of the neural tissue, while using lower stimulation thresholds and offering higher spatial selectivity [14], typical stimulation pulses comprise two phases. The first phase, the cathodic phase, is used to transfer the necessary amount of charge for stimulation, followed by the second, the anodic phase, to reverse this process.

The charge transfer that occurs during stimulation results in chemical reactions at the electrode-tissue interface (ETI), which can be reversible or irreversible [15]. Irreversible reactions, also known as faradaic processes, can cause damage to both the electrode and the surrounding tissue [16]. These reactions include water reduction at the negatively charged cathode (water is reduced to hydrogen gas) and water oxidation at the positively charged anode (water is oxidised to oxygen gas). By adding the second phase to the stimulation pulse, the reversible reactions can be neutralised, while the irreversible reactions result in an accumulation of charge across the ETI. In the absence of a second phase, none of the reactions are reversed and therefore, more charge accumulates at the ETI, as illustrated in Fig. 2.4.

The chemical processes that take place during stimulation at the ETI are modelled electrically by a simplified electrical circuit model, as depicted in Fig. 2.5. This equivalent model consists of the spreading resistance R_S , representing the resistive behaviour of the tissue, the double layer capacitance C_{DL} , representing the reversible charge transfer across the interface, and the faradaic (or charge transfer) resistance R_F , representing the irreversible faradaic charge transfer through reduction-oxidation (redox) reactions [17]. Electrodes dominated by reversible currents are classified as polarisable, whereas those influenced by irreversible currents are non-polarisable [17]. Finally, V_{eq} represents the equilibrium (or half-cell) potential that is present

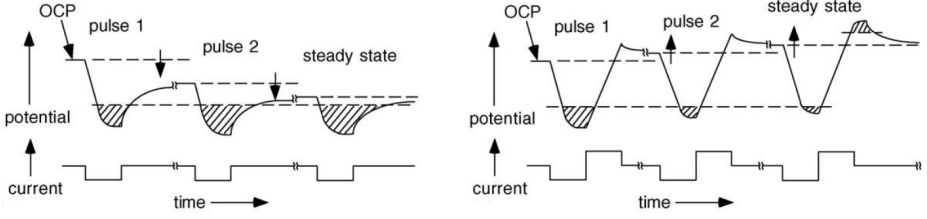


Figure 2.4: Effect of a monophasic (left) and a biphasic (right) pulse on the electrode potential, indicated in the striped area. The open circuit potential (OCP) indicates the potential at the beginning of the stimulation. During a monophasic pulse, the pulse potential successively moves negative until all injected charge goes into irreversible reactions, as indicated by the shaded areas. During a biphasic pulse, the pulse potential successively moves positive until the same amount of injected charge is lost in irreversible reactions during both phases, again as indicated by the shaded area. Figure adapted from [15].

at the ETI even when no stimulus is applied to the electrode [17]. Fig. 2.5 shows a typical pair of electrodes used for stimulation, a working electrode (WE) and a counter electrode (CE).

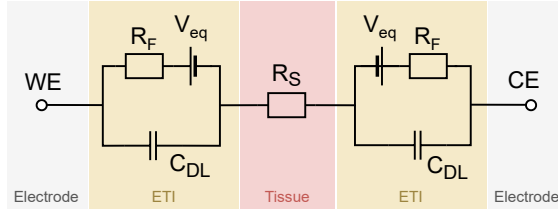


Figure 2.5: Simplified electrical circuit model of the electrode-tissue interface (ETI), consisting of the spreading resistance R_S (tissue behaviour), the double layer capacitance C_{DL} (reversible charge transfer), the faradaic resistance R_F (irreversible charge transfer) and the equilibrium or half-cell potential V_{eq} .

The amount of charge lost in irreversible processes that accumulates at the ETI at the end of the biphasic pulse leads to the build of a residual DC voltage, here described as the electrode offset voltage V_{offset} . This electrode offset voltage appears due to mismatches or offsets in the output signal of the stimulator, and/or due to the non-linear nature of the ETI [18]. Fig. 2.6 illustrates this voltage buildup at the ETI when stimulating with a biphasic current or voltage pulse. Is more charge transferred during one phase of the biphasic pulse compared to the other, the C_{DL} is charged accordingly. If the period between the pulses is insufficient for a gradual and slow discharge, the offset voltage increases with every stimulation period. As the voltage across the ETI increases, chemical species are created due to irreversible reactions that occur. When this voltage reaches a certain safety window, known as the water window, electrolysis occurs. The water window is defined through the oxidation

and reduction potentials of an electrode versus a reference (typically a silver/silver chloride (Ag/AgCl) electrode), and reaching it is undesirable as damage to the electrode and the tissue is expected [16]. Therefore, achieving charge balancing (CB) across the ETI and, thus, maintaining a stable offset voltage within specified limits, is a critical aspect of the stimulator system design for safe neuromodulation.

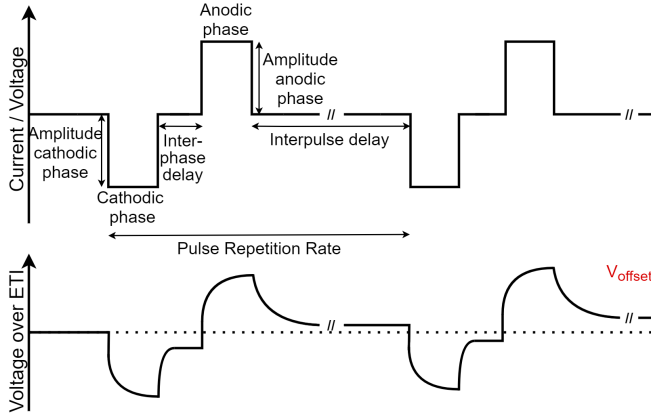


Figure 2.6: Conventional biphasic stimulation pulse (current or voltage) and corresponding voltage over the electrode-tissue interface (ETI), with the electrode offset voltage V_{offset} indicating the undesirable charge buildup at the ETI.

Different methods have been implemented to maintain the V_{offset} as low as possible and achieve CB across the ETI. Depending on the actions taken to remove any excess charge and lower V_{offset} , CB systems are divided into two categories: passive and active.

2.2.2. PASSIVE CHARGE BALANCING

A passive CB method does not actively monitor the voltage at the electrode site and passively steers any excess electrode potential towards zero [19]. A widely used passive CB method is electrode shorting, where the stimulating electrodes are grounded after every biphasic pulse, allowing them to discharge [20], which, however, due to the time constant of the ETI, can be insufficient for larger V_{offset} or higher pulse repetition rates. The placement of a coupling capacitor or high-pass filter between the stimulator and the stimulating electrode is another common passive CB method, ensuring that no DC will flow through from the stimulator to the electrode, though [21] discusses that it introduces an additional offset voltage. Even though passive CB methods are easy to implement and reliable, they are often insufficient, given the non-linear behaviour of the ETI.

2.2.3. ACTIVE CHARGE BALANCING

During active CB, feedback from the ETI is required, and a compensation charge is injected based on the received feedback. Active CB systems measure the electrode offset voltage either continuously [22] or in a discrete-time manner by sampling after the biphasic pulse [23]. A continuous measurement system must be capable of handling high voltages and should provide a high input impedance to prevent current leakage into the system instead of into the electrode. This is not necessary if the system measures in a discrete-time manner and is disconnected during the stimulation pulses.

Active CB methods will either manipulate the stimulation pulse directly or introduce a complementary pulse injected in parallel to the stimulation pulse to counteract any unwanted charge accumulation. The most intuitive method for injecting a complementary pulse is the pulse insertion technique, as described in [24], where V_{offset} is sampled right after the stimulation pulse, and small charge packages are injected to bring it within a predefined safety window. The sampling and injecting are continued until V_{offset} falls within that window, here set at ± 50 mV. Another option is presented in [23], where V_{offset} is sensed after each stimulation cycle, and a corrective current is applied to the electrodes should the measured voltage value not fall within a predefined range.

A manipulation of the stimulation pulse to attempt CB involves adjusting its parameters, such as the pulse width or amplitude, provided these parameters can be modified. In this respect, [18] actively monitors the voltage at the electrode site during stimulation and then tailors the duration of the second phase of the biphasic pulse accordingly. Alternatively, [25] explores in simulations the use of a Proportional-Integral-Derivative (PID) control scheme to adapt the pulse width, while [26] proposes an analog implementation of a PI controller to adapt the amplitude of the charge-compensating second phase.

2.3. DEVICE POWERING

2.3.1. BATTERIES

Conventionally, neural implants use batteries to supply the necessary power for operation, with many commercial systems serving as examples (e.g., systems by Medtronic, Abbott, Boston Scientific) [27], given their technological maturity, as well as their general availability and ease of access [28]. Though they provide a continuous and adequate power source, they are limited by their large and bulky form factor and their relatively short lifespan. Even with current battery lives ranging between 5 and 15 years (e.g., for pacemakers, 7 to 12 years in single-chamber and 5–10 years in dual-chamber models) [29], the inevitable battery replacement comes with the risks of a surgical procedure and interruption of therapy. Furthermore, the large size and weight of batteries are a limiting factor regarding the miniaturisation of neural implants [27]. While simultaneously considering the safety hazard that the contact of a battery and the biological tissue poses, a rigid, hermetically sealed

package is often necessary to house them. Such casings, however, are much stiffer than biological tissue and can cause foreign body reactions and inflammation [28].

Recent attempts at overcoming these constraints, while offering advanced solutions in the design of implantable bioelectronics, include the development of battery-less, wirelessly powered alternatives for applications where the delivery of the therapy is not time-critical or life-sustaining. Such alternatives will be easier to miniaturise and avoid the risks that come with battery replacements, while having a reduced environmental footprint [30]. Some of the most widely applied wireless power transfer (WPT) schemes include near-field power transfer (inductive coupling and magnetic resonant coupling), mid-field power transfer, far-field radio frequency (RF) power transfer, photonic power transfer and ultrasound power transfer [28, 31, 32], as depicted in Fig. 2.7.

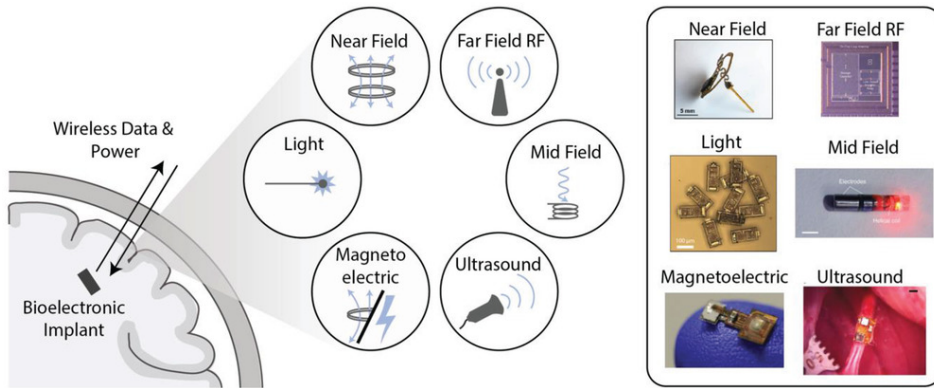


Figure 2.7: Different wireless power transfer strategies, including ultrasound power transfer, near-field, mid-field and far-field RF power transfer, and photonic power transfer. Figure taken from [31], © 2021 The Authors.

2.3.2. WIRELESS POWER TRANSFER TECHNIQUES

Near-field power transfer

Near-field WPT, initially demonstrated by Nikola Tesla [33], uses electromagnetic waves to transfer energy between a transmitting and a receiving coil through inductive coupling [28, 31, 32]. This method can transmit power over smaller distances and in the presence of obstacles between the coils, and is implemented in numerous applications, with a transmission efficiency reaching values as high as 88% [34]. Still, inductive coupling suffers from misalignment sensitivity and a limited transmission distance [35], which can be critical for powering implantable devices. Both the transmission efficiency and distance can be enhanced by adopting a matching resonance frequency for the transmitting and receiving coils [28, 31]. When tuned at the same resonance frequency, the power transfer between the two coils increases significantly, allowing for larger transmission distances and positioning errors [32]. Typically, near-field power transfer is performed at 13.56 MHz given the

frequency's low biological tissue absorption and the fact that it aligns with near-field communication (NFC) standards, while supporting power transfer levels of up to 4 W - deeming the implementation of wireless communication along with power transfer at the same frequency possible [28].

Far-field RF power transfer

Again using electromagnetic waves, far-field power transfer transmits power from an external RF antenna to a receiving antenna [31]. Far-field WPT operates over longer distances and at higher frequencies (from high-megahertz to gigahertz) compared to near-field WPT, while advanced antenna designs offer the possibility to operate over multiple resonant frequencies simultaneously [27]. However, far-field power transfer demonstrates a much lower efficiency [35], given its high sensitivity to antenna misalignment. The transmission efficiency can be further affected by interference caused by environmental obstructions [28] that reflect RF waves. These interferences between the transmitted and reflected RF waves can, in some cases, create hotspots, leading to potentially high specific absorption rates (SARs) and tissue overheating [27, 28].

Mid-field power transfer

A strategy that combines aspects of the near-field and the far-field power transfer schemes is mid-field power transfer, typically operating at frequencies in the low-GHz range [31, 36]. This range is selected to maximise the power transfer efficiency in deep-seated implants, where the optimum value is selected based on the exact implant depth, the implant size and the type of tissue layers separating the transmitter from the receiver [36, 37]. Furthermore, by appropriately designing the transmitting source, the emitted waves concentrate at the receiving coil [36], thus maximising the power transfer efficiency without significant attenuation [37]. Still, the power delivered is in the mW range, limiting the applications that can employ mid-field power transfer [36].

Photonic power transfer

Photonic WPT represents another means of transferring power through electromagnetic waves, though at different wavelengths than near-field and far-field WPT and in the form of visible and near-infrared light [28, 31]. Here, photovoltaic cells act as receivers, offering the great advantage of their miniaturisation potential to sub-mm areas [31]. Given the low transmission efficiency of optical emitters and the scattering and absorption of the light by the biological tissue, photonic power transfer requires an intense light emitter that is precisely directed towards the photovoltaic receivers [27, 31]. Should this be the case, photonic power transfer represents a fitting choice for low-power, sub-mm-sized neural implants, that are positioned only a few mm below the skin surface [31].

Ultrasound power transfer

Ultrasound power transfer uses acoustic waves, emitted at high frequencies, to transmit energy [28, 31]. The ultrasound transducers used as transmitters and receivers convert energy from the acoustic to the electrical domain and vice versa.

While the most common form of acoustic transducers are piezoelectric sensors, their high manual labour costs and constitution of toxic metals have opened up the way for the development of micromachined ultrasound transducers, such as capacitive and piezoelectric micromachined ultrasound transducers (CMUTs and PMUTs, respectively) [38, 39].

The lower acoustic velocity of acoustic waves compared to electromagnetic waves enables the design of smaller transducers with higher spatial resolution [38, 40]. Furthermore, the lower attenuation of acoustic waves in biological tissue enables the transfer of power to deeper located mm-sized neural implants, reaching implantation depths as far as 7 cm [41]. As a downside, when transferring power through ultrasound, an impedance mismatch between the different materials and tissues/layers can result in reflections and reduced transmission efficiency. To compensate for this, the acoustic transmitter needs to be placed directly on the tissue (sometimes adding a gel medium to establish full contact) [31], while the acoustic receiver is equipped with one or multiple layers that aim at matching the acoustic impedance of the transducer to that of tissue [40]. To further enhance the effective acoustic impedance of the receiver, an electrical impedance matching circuit can be included to match the impedance of the transmitter to that of the load circuitry [40]. Furthermore, acoustic transmission is prone to misalignment errors [28]. To overcome this, single transducers can be replaced by transducer arrays, capable of focusing and steering the ultrasonic beam towards their target [42, 43].

2.4. INCREASING ENERGY EFFICIENCY & STIMULATION EFFICACY

2.4.1. SELECTIVE STIMULATION

While the electrical stimulation of neural tissue has proven to be a successful means of treating neurological diseases and disorders, current neuromodulation therapies still suffer from a lack of stimulation precision, leading to unwanted side effects [44–46]. Conventionally, the electrodes used to interface with the tissue are larger in size and cover a greater area beyond the targeted tissue, often stimulating neighbouring regions. Such designs cannot safely and effectively modulate the neural tissue, calling for the development of more precise and selective neural interfaces [46–49].

As illustrated by the general anatomy of a peripheral nerve targeted during peripheral nerve stimulation (PNS) (see Fig. 2.8A), the nerve is a structure that consists of multiple fascicles, each performing a different function. To enhance stimulation selectivity and provide improved therapeutic effects, the targeted stimulation of specific nerve fascicles is needed [44, 46, 48, 50]. The most common practice of stimulating a peripheral nerve directly at its surface is through cuff electrodes that wrap around the nerve, as seen in Fig. 2.8C. However, such cuffs stimulate whole areas of the nerve's cross-section and cannot precisely address individual fascicles [48].

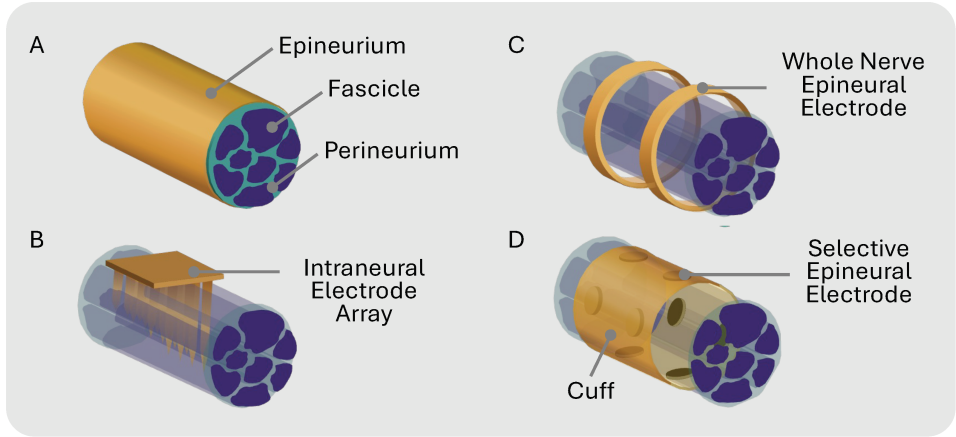


Figure 2.8: *a) General anatomy of a peripheral nerve. b) Penetrating (intraneural) electrode array. c) Cuff electrode array. d) Multi-contact cuff electrode array. Figure taken from [48], © 2024 The Authors.*

More promising results in terms of selectivity have been demonstrated through the use of nerve penetrating (intraneural) electrodes, as depicted in Fig. 2.8B. Notable examples include the Utah slanted electrode array (USEA) [51] and the transverse intrafascicular multi-channel electrode (TIME) [52]. While both designs achieved an improved selectivity, they need to penetrate the nerve, making them highly invasive while requiring complex implant procedures [53]. A non-penetrating alternative that enhances selectivity, but still requires the alteration of the nerve's form, is the flat interface nerve electrode (FINE) [54]. This electrode reshapes and flattens the nerve, spreading its fascicles and thus allowing them to come closer to the surface for a better connection and more targeted activation.

Multi-contact cuff electrodes offer enhanced selectivity and the possibility of addressing individual nerve fascicles through a larger number of contacts (see Fig. 2.8D), while maintaining the structure of the nerve intact. The individual contacts to stimulate the area of interest can be independently selected, while choosing from a variety of combinations for the active anode and cathode positions and placement [55], as depicted in Fig. 2.9. Through their use, many applications have successfully demonstrated a selective activation of individual fascicles and an improved therapeutic outcome with fewer off-target side effects [48, 56–58]. Achieving such precision and enhanced stimulation selectivity through multi-contact cuff electrodes requires appropriate hardware that can selectively and independently drive the channels that correspond to the individual electrode contacts.

2.4.2. NON-RECTANGULAR WAVEFORM STIMULATION

Rectangular stimulation pulses have been the gold standard in clinical neuromodulation applications. Nonetheless, recent studies have been investigating the

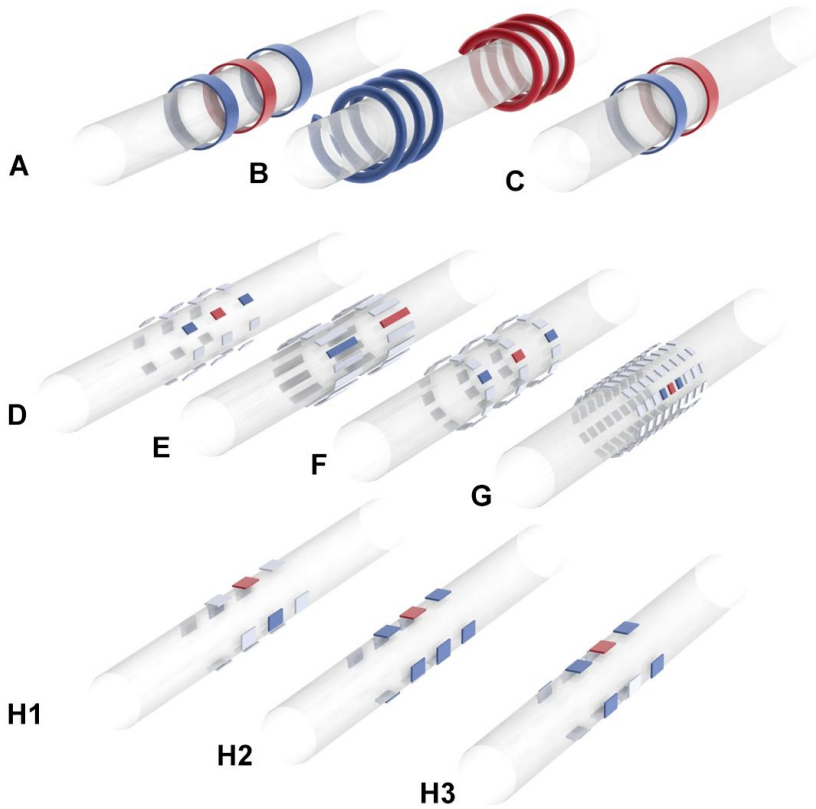


Figure 2.9: *Different electrode array geometries, here particularly on the application of selective VNS. While traditionally ring or helical electrodes are used, recent studies are employing smaller contacts at a higher number that can allow for more targeted stimulation. Figure taken from [46], © 2021 Fitchett, Mastitskaya and Aristovich.*

use of non-rectangular stimulation pulses as a means of increasing stimulation efficiency and safety, by requiring less charge to activate the targeted area [59]. Mostly through computational studies that use complex neuron models, scientists have reported increased efficiency in non-rectangular pulse shapes compared to rectangular ones [60–63]. Fig. 2.10 provides an overview of the most commonly investigated non-rectangular pulse shapes, including ramped, triangular, Gaussian, sinusoidal and exponential.

Aside from increasing stimulation efficiency, non-rectangular waveforms have been shown to also increase stimulation selectivity [45, 59]. Specifically, non-rectangular pulses have the potential to increase selectivity by leveraging the diversity of electrophysiological membrane properties [64] or activating specific fibre types within a nerve fascicle [65].

While the use of non-rectangular stimulation pulses demonstrates a higher efficiency and selectivity compared to the conventional rectangular ones, no single

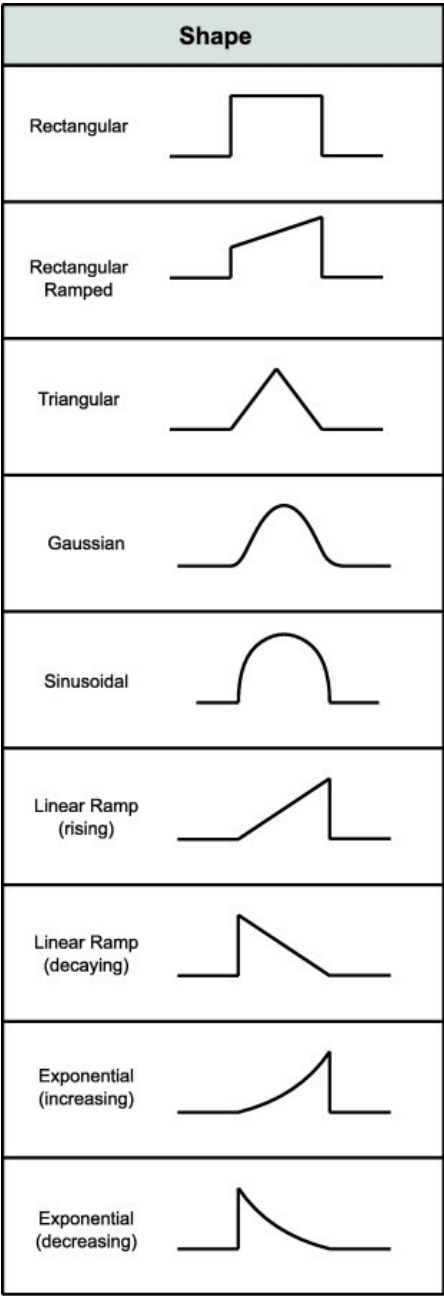


Figure 2.10: Most frequently investigated non-rectangular waveform shapes for optimising stimulation efficiency. Figure adapted from [59].

shape has been found to be simultaneously the most energy-, charge-, and power-optimal [61]. Furthermore, what is often overlooked in literature is the fact that non-rectangular pulses require a higher compliance voltage due to their shape, as they need a higher amplitude to deliver the necessary amount of charge for activation [66]. Consequently, as the required peak current increases, any energy savings inevitably decrease. Therefore, it is essential to adapt current neuromodulation equipment with architectures that support the energy-efficient generation of non-rectangular stimulation pulses.

2.4.3. ADAPTIVE POWER SUPPLIES

Conventional neuromodulation devices suffer from reduced power efficiency, since they are designed to provide a constant supply that is high enough to fulfil the maximum power needs of each application. Should a lower supply level suffice to achieve the intended activation (e.g., a lower pulse amplitude is needed, the targeted area is easier to activate), any excess power is unnecessarily dissipated, as illustrated in Fig. 2.11. This issue becomes more prominent in the case of multichannel stimulators, where all stimulation channels share the same supply rail. In this case, any channel that requires a lower supply level is operated sub-optimally. To overcome this, recent studies have proposed adaptive power supplies as a means to dynamically scale the supply voltage according to the instantaneous requirements, thus increasing energy efficiency [67–72], as demonstrated in Fig. 2.12.

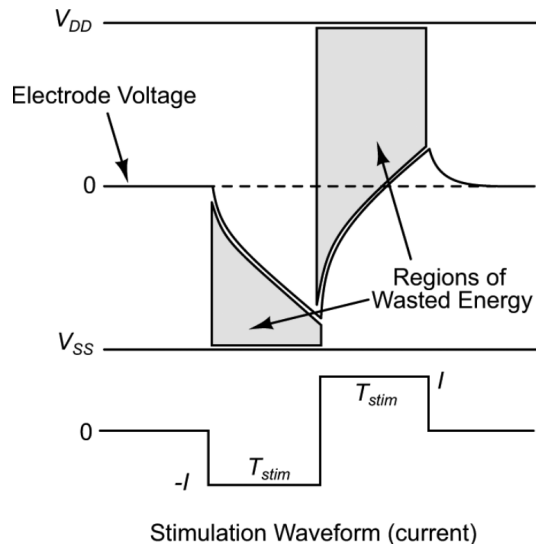


Figure 2.11: The shaded area represents the excess power that is unnecessarily dissipated in the case of constant current stimulation (CCS) and a constant supply. Figure taken from [70], © 2012 IEEE.

One approach involves scaling the supply voltage by modulating the wirelessly

received AC signal [68, 69]. This, however, comes at the cost of a less efficient wireless link, as part of the transmitted energy will be rejected if it is not momentarily needed. Alternatively, an adaptive DC/DC converter can be used to generate multiple supply rails, either through inductive buck/boost converters [70, 72] or through switched-capacitor charge pumps [67, 71, 73, 74]. Still, inductive buck/boost converters come at the expense of bulky off-chip inductors, while switched-capacitor charge pumps offer limited output resolution [66]. These limitations underscore the need for the design of an adaptive power supply that enhances energy efficiency while meeting the individual supply needs of each channel in multichannel stimulator designs. Additionally, combining an adaptive supply with non-rectangular waveform stimulation can further increase energy savings [75], aiding in the advancement of designs for low-power, miniaturised neural implants.

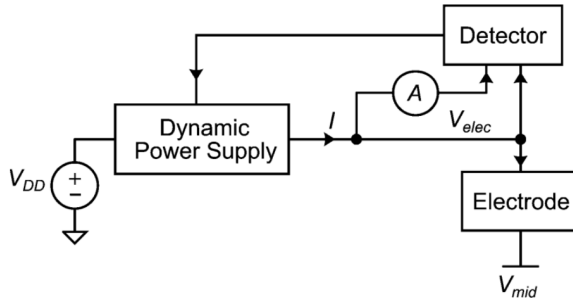


Figure 2.12: *Basic concept of a stimulator using dynamic voltage scaling, where the electrode current and voltage are monitored to adapt the supply accordingly. Figure taken from [70], © 2012 IEEE.*

2.5. STATE OF THE ART IN EXPERIMENTAL NEUROMODULATION PLATFORMS

The continuous advancement in technology and neuroscientific knowledge often calls for the development of new hardware to explore novel possibilities in the design and functionality of neural implants. To this end, many research groups have designed and implemented neuromodulation systems and platforms for use in experimental settings, addressing needs that current devices do not meet, such as programmable stimulation, physiological parameter recording for closed-loop neuromodulation, multichannel operation, and wireless powering and communication. This section provides a small overview of relevant designs, with the developed devices depicted in Fig. 2.13.

Neuro-stack, a wearable bidirectional system as shown in Fig. 2.13a, is developed in [76] and can record single-neuron and local field potential activity of deep brain areas for closed-loop neuromodulation. It is intended for basic and clinical neuroscience studies, with a small form factor for freely moving behaviour. Neuro-stack can record

from up to 256 contacts, resulting in a total of 128 monopolar or bipolar recordings. It offers programmable stimulation to up to 32 contacts simultaneously, with adjustable current amplitude, frequency, and pulse shape, among other parameters. Finally, it supports both wired and wireless operation modes, being controlled and powered via a USB connection or remotely controlled through a secure local network, with a battery providing the power. While Neuro-stack provides an effective and portable solution compared to similar bidirectional devices, it still integrates hardware ICs, which were developed by [76] during earlier research, and a replication of the design would require the replication of this hardware.

A multichannel wireless neurostimulator designed for use in animal experiments is developed in [77] using only commercially available components (Fig. 2.13b). The stimulator has a small form factor and can be carried by the animal in a small backpack, allowing them to move freely. The stimulator is battery-powered and can communicate wirelessly with a host computer in real time through an RF link. It offers programmable stimulation to a maximum of 8 electrodes and can be adapted to support a connection to different microelectrode arrays. When the device is not in stimulation mode, it automatically enters low-power mode to save battery. While the developed neurostimulator is easily reproducible and offers flexibility in defining the stimulation parameters and a multichannel operation, all electrodes receive the same settings, which limits the paradigms that can be tested. Furthermore, the introduction of charge balancing measurements would increase the safety of the device.

A portable multichannel neurostimulator was developed in [78] that can deliver constant current stimulation, with or without anodic bias, to 16 channels, while simultaneously recording the resulting voltage transients at the electrodes to monitor their electrochemical safety (Fig. 2.13c). It can provide monophasic or biphasic (symmetric or asymmetric) stimulation with current levels up to $160\mu\text{A}$, and the recorded voltage transients are used to estimate the level of polarisation on the stimulating electrode to identify the point beyond which irreversible electrochemical reactions take place. It can communicate wirelessly through Bluetooth with a graphical user interface (GUI) on a laptop and is battery-powered. The neurostimulator is implemented using only off-the-shelf components, making it accessible to other researchers. However, given the intended application, it does not provide higher flexibility in the multichannel operation, such as individually addressing the outputs.

Following the need for investigation of new deep brain stimulation (DBS) paradigms in preclinical settings, [79] developed a miniature, low-power device that can be comfortably carried by a small animal (Fig. 2.13d). It provides high flexibility in defining the stimulation waveform by adjusting its shape, frequency, pulse-width and amplitude. The device supports non-rectangular waveform stimulation, in addition to the standard rectangular shape, and features an active CB scheme for safe operation. It supports a connection to a single channel, stimulating with amplitudes between $\pm 200\mu\text{A}$ and at a frequency of up to 10 kHz. The developed stimulator is battery-powered, and the stimulation can be activated or deactivated by placing an external magnet in the vicinity of an integrated Hall-effect sensor. However, while

providing a highly programmable output, this device does not support multichannel operation.

The neurostimulator depicted in Fig. 2.13e is a miniaturised device to be used in a research context using VNS as a means of treatment against drug-resistant epilepsy [80]. The device is designed for use in a preclinical experimental setting, utilising inexpensive commercial components. It is battery-powered, can be programmed through a USB connection, and is continuously kept in a low-power state, activated by an external magnetic switch. The stimulator provides an affordable implantable alternative to commercial devices for VNS. Nevertheless, it does not offer flexibility in the pulse sequence programmability or support multichannel stimulation.

A neurostimulator able to generate neural code-based, precise, asynchronous electrical stimulation pulses is developed in [81], as an attempt at enabling neural code-based stimulation in DBS applications (Fig. 2.13f). The system provides constant current biphasic pulses, with arbitrary temporal patterns, to 32 electrodes via multiplexing. It allows for stimulation and recording from the same electrode to enable closed-loop neuromodulation and includes a stimulus artifact suppression technique. The device was built using commercially available chips and components to provide a cost-efficient and reproducible design, and is powered by a battery. The device does not include further CB measurements beyond the generation of symmetrical biphasic pulses, as the intended application requires a sparse and low pulse repetition rate, with the electrodes being grounded after each stimulation pulse; therefore, no excess charge buildup is expected. The system provides the required flexibility for the intended application; however, it otherwise has a limited pulse sequence programmability and a multichannel operation that uses the same settings for every electrode.

The HybridVNS, a closed-loop VNS system, able to perform an electroencephalogram (EEG) recording through a wearable EEG recorder while simultaneously stimulating the vagus nerve through an implantable VNS implant to treat refractory epilepsy, is developed in [82]. The implantable stimulator, depicted in Fig. 2.13g, integrates a pulse generator and an ETI impedance extractor to determine whether the attached stimulating electrodes are in contact with the tissue and there has not been any damage to the electrode leads. It can be powered wirelessly through an inductive coupling link and communicates via Bluetooth. It includes a temperature sensor that notifies of unwanted tissue temperature increases during stimulation or powering. The device is implemented using off-the-shelf components, is battery-powered, and has a low-power design to increase battery lifetime. Still, it offers little programmability in the stimulation parameters and does not support multichannel operation.

Each of the presented systems is intended for a different neuromodulation application and developed accordingly to fit the application's needs. They are all developed for experimental purposes and are mostly considered for preclinical settings. The developed stimulators, except for [76], are built around a microcontroller unit and use commercially available components to allow for applicability, thus increasing accessibility by other research labs. Still, many designs are battery-powered and do not consider a future implementation in an implantable version during

their development process. Furthermore, some of the presented examples have to be directly programmed, which would require expert knowledge and would not be easy to handle by non-technical personnel. Finally, many devices do not support multichannel operation or apply the same stimulation settings to every output.

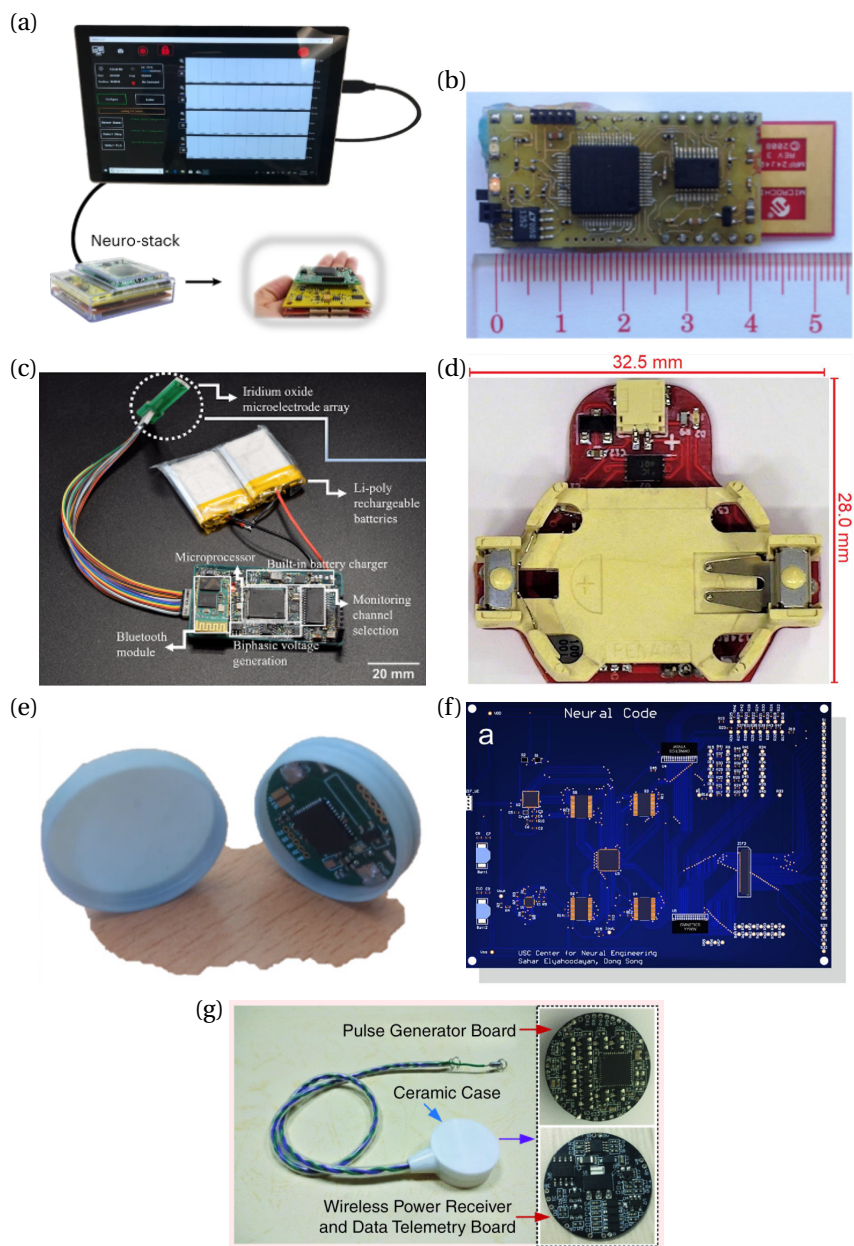


Figure 2.13: Exemplary overview of state-of-the-art devices in experimental neuromodulation applications. Figure (a) adapted from [76], under the terms of a Creative Commons Attribution 4.0 International License <http://creativecommons.org/licenses/by/4.0/>. Figure (b) adapted from [77], © 2013 IOP Publishing Ltd. Figure (c) adapted from [78], © 2022 The Author(s). Figure (d) adapted from [79], © 2019 Adams et al.. Figure (e) adapted from [80], © 2022 The Authors. Figure (f) adapted from [81], © 2019 Elyahoodayan, Jiang, Xu and Song. Figure (g) adapted from [82], © 2022 IEEE.

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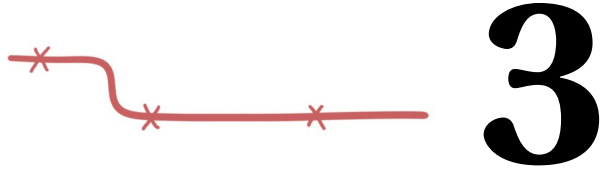
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DESIGNING NEUROMODULATION HARDWARE FOR A CLINICAL SETTING

*However great your dedication,
you never win anything on your own.*

Rafael Nadal

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3.1. INTRODUCTION

When designing neuromodulation hardware with the intent of using it in a clinical (human) setting, it is essential to ensure a safe, accommodating and user-friendly design. Such hardware, when not commercially available as a whole, is typically a custom design based on the needs and requests of the physicians and general specialists (doctors, neuroscientists etc.) involved in the trials. The main concerns, therefore, lie in fulfilling the relevant trial requirements while providing a final device that is safe for both the participants of the trial as well as the personnel involved in conducting them. Furthermore, the final device needs to be relatively uncomplicated to handle and understand by the clinical personnel, whose expertise does not lie in the core electronic design of the hardware.

The development of a dorsal root ganglion (DRG) stimulator system intended for use in early clinical trials for motor recovery after spinal cord injury (SCI), as described in the sequel of this thesis, is an attempt at following these guidelines. It allows for independent control of multisite/multilevel bilateral (on both sides of the spinal cord) stimulation, can supply a high output current of 25.4 mA, and has the ability to program pulse sequences similar to actual locomotion patterns. These characteristics ultimately provide the required versatility for examining the effects of DRG stimulation on locomotion recovery, which is lacking in currently available commercial systems. The device is designed using commercially available components to ensure reproducibility by other research labs and to facilitate the critical approval process for use in a clinical research environment. Throughout the design phase, essential safety considerations were taken into account. Despite being common practice for commercially developed systems, such considerations are rarely reported in the scientific literature.

Building upon this design, and in an attempt to increase the patient safety of this and any similar device, given the direct contact with neural tissue, a broad frequency range charge balancing system was designed to be used as an add-on system for neural stimulators. It operates independently of the stimulator timing by continuously sensing the offset voltage and applying a corrective current to the electrode, thus using an offset compensation technique. To ensure its stand-alone capability, the system is battery-powered and includes a safety and start-up circuit. Electrical measurements verified the functionality of the circuit.

3.2. DORSAL ROOT GANGLION (DRG) VERSATILE STIMULATOR PROTOTYPE DEVELOPED FOR USE IN LOCOMOTION RECOVERY EARLY CLINICAL TRIALS

In the event of spinal cord injury (SCI), the neuronal pathways between the brain and the rest of the body are damaged. As a consequence, many physiological processes such as motor control, sensory feedback or autonomic functioning are (partially) disrupted, leading to a loss of functional independence [3] or an overall loss in quality of life [4]. No clinical treatment is available for complete recovery after

an SCI, however, there are attempts at recovering locomotion [5]. In an experimental setting, neuromodulation of the spinal pathways below the site of injury seems to be one of the most promising approaches [5]. epidural spinal cord stimulation (eSCS) has been one of the most common applications and offers the ability to reinstate voluntary motor control in patients with (motor complete) SCI, with or without concomitant rehabilitation [6], [7], [8].

Recently, a relatively new target for neuromodulation in SCI has surfaced. By targeting the dorsal root ganglion (DRG), researchers have shown the ability to evoke strong, long-lasting muscle responses leading to knee extension [9] (Fig. 3.1a-c). Compared to eSCS, DRG stimulation – which has already been established for chronic pain treatment [10] – has the potential to target relevant muscle groups in a more selective manner [9], [11], [12]. In order to be truly applicable in the context of SCI, this single DRG-level proof-of-principle needs to be expanded to a multi-level approach, targeting multiple levels of DRG leads in a sequence that would mimic a physiological, locomotive pattern. However, currently available commercial devices are tailored to the context of chronic pain treatment and do not allow for this type of versatile, multi-channel stimulation.

This work introduces the development of a multichannel external pulse generator (EPG) prototype system, designed to target up to 16 channels independently, to further explore the effects of multi-level DRG stimulation on motor recovery after SCI during early clinical trials. The prototype system comprises the external stimulating hardware, interfacing with eight (8) implantable multi-electrode leads, and a suitable user interface. It is created by utilising commercially available components to ensure reproducibility by other research labs and to expedite the required approval procedure necessary to be obtained prior to inclusion in early clinical trials.

3.2.1. PRIOR ART AND CURRENT NEEDS ON DRG STIMULATION

In their 2020 paper [9], Soloukey et al. for the first time demonstrate how L4-level DRG stimulation is able to evoke reproducible muscle response in the upper leg muscles of five patients with motor complete SCI. These responses result in a strong, long-lasting extension of the leg in the knee joint. The authors describe how DRG stimulation could evoke both dynamic (high-amplitude stimulation, Fig. 3.1b) as well as isotonic (high-amplitude, high-frequency stimulation, Fig. 3.1c) muscle responses, here displayed using the electromyography (EMG) responses of the vastus lateralis (VL) muscle as an example. For this study, the DRG leads (part of the Abbott[®] Proclaim[™] DRG neurostimulator system) were placed percutaneously under X-ray guidance (Fig. 3.1d) on the bilateral L4-level DRGs. Each lead consists of 4 individually addressable electrode points. The complete commercially available Abbott[®] DRG stimulation platform employed for this study, including the implantable pulse generator (IPG), providing a connection to a maximum of 4 DRG leads, and the clinician interface on a tablet, is illustrated are Fig. 3.1e.

To achieve locomotion-like stimulation, several stimulator characteristics need to be considered, in parallel to systems tailored for preclinical eSCS studies [13], [14], [15], [16]. While the stimulator by Abbott[®] provides a physical connection

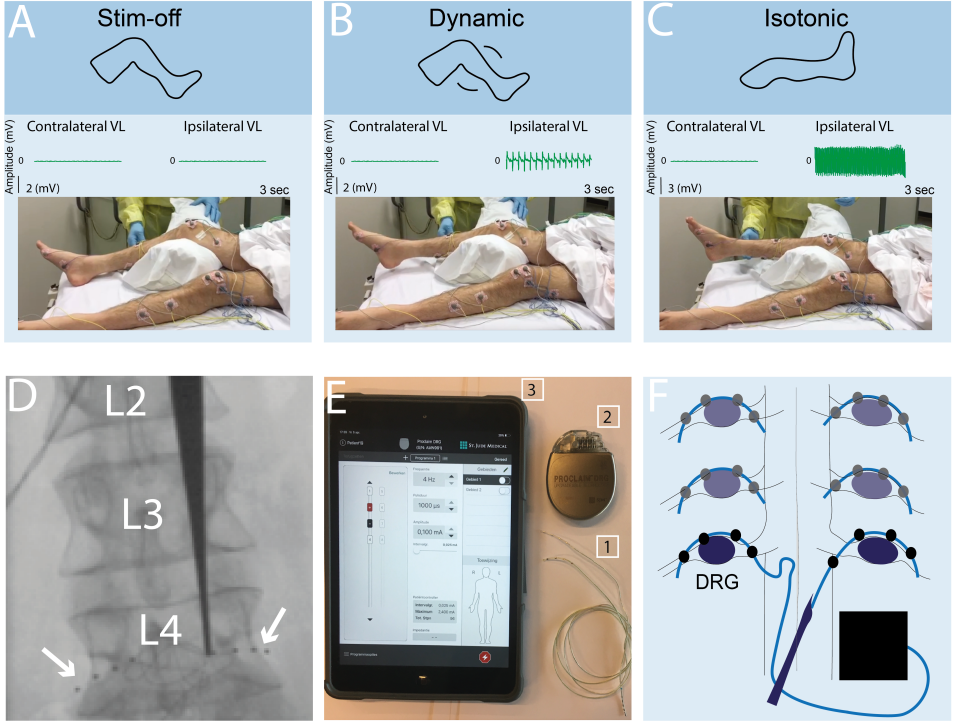


Figure 3.1: Overview of the status-quo of the DRG as a novel target for neuromodulation. (a-c) demonstrate how DRG stimulation could evoke dynamic and isotonic muscle response ipsilateral to the side of stimulation. (d) shows an intra-operative X-ray image of the bilateral DRG lead placement. (e) gives an overview of the Abbott[®] DRG stimulation device (ProclaimTM DRG). (f) provides an example of multi-level DRG stimulation and lead placement, which would require a new type of multichannel stimulator (black box).

to a maximum of 4 leads, it cannot address them simultaneously, but in a time-multiplexed manner. However, multiple DRGs will need to be accessed bilaterally and at once, to recruit the right muscle groups at the right moment in the locomotion cycle. For the purpose of multilevel DRG stimulation, no such pulse generator is currently commercially available. Fast switching times between the stimulating leads and the possibility of interleaved stimulation across multiple leads to allow for left-right alteration or agonist-antagonist recruitment, can also enhance locomotion-like stimulation. More complex stimulation patterns (e.g. ramping the current up/down instead of simply turning it on/off, delays in the pulse sequence, skipping a pulse) can increase the flexibility in programming the pulse sequence and generating a more realistic locomotion pattern. Conventional EPGs have a maximum current output of 6 mA. However, based on previous studies [9], this range can fall short regarding motor recruitment. Having a larger current output range (within safety constraints) may facilitate stronger muscle contraction.

3.2.2. SYSTEM ARCHITECTURE

A block diagram of the complete system is presented in Fig. 3.2. The prototype stimulator is a non-CE-marked multichannel device, which can drive multiple leads concurrently to facilitate faster, sequential stimulation. To ensure reproducibility by other research labs, only commercially available components were used.

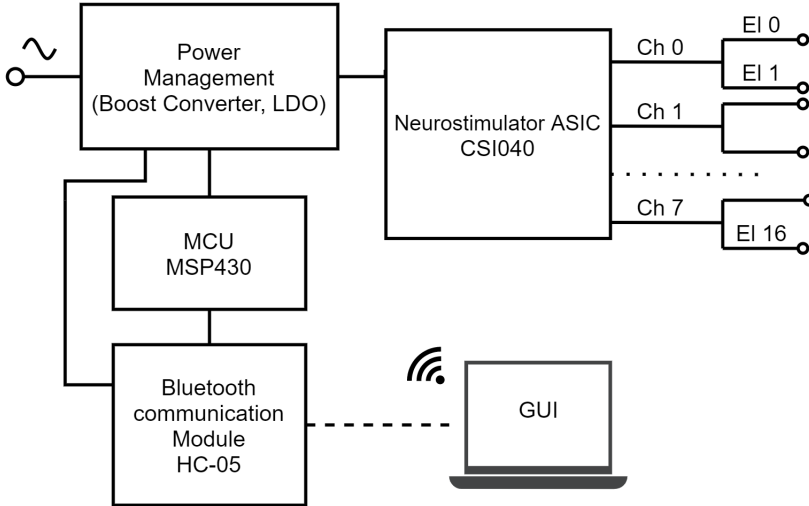


Figure 3.2: Block diagram of the stimulator system proposed for this study. An MCU programs the stimulation parameters, a Bluetooth module communicates with any external components (i.e., a GUI on a local PC). 8 independent stimulation channels are able to flexibly address a total of 16 electrodes concurrently.

The core element of the stimulator prototype is its highly programmable current sink/source application specific integrated circuit (ASIC), CSI040, developed by Cirtec Medical [17]. It features 16 independent, 7-bit programmable current outputs. The CSI040 ASIC is mounted on the CSI062 board, a demonstration board for the CSI040 ASIC, also developed by Cirtec Medical [18]. The device provides electrical pulses that will be applied to the DRG through the CE-marked DRG leads from Abbott® (Proclaim™ DRG). Each DRG lead is equipped with 4 electrodes, and given the 16 outputs of the stimulator, a maximum of 8 leads in total can be stimulated simultaneously when using 2 of the 4 electrodes of each lead (which can be easily expanded to all 4 with the addition of a demultiplexer). The leads are connected to the prototype through properly fitted connectors, which were constructed in-house using the A22041-001 connectors from Omnetics.

A user is able to select the parameters for each stimulation channel, such as pulse width, pulse repetition rate, stimulation on/off times, stimulation current, and amplitude ramping, all of which are fully programmable, via a graphical user interface (GUI) on a local computer. These parameters are wirelessly communicated via a Bluetooth module (HC-05 by ITeard Studio) to the microcontroller unit (MCU)

(MSP430I2041TRHBT, Texas Instruments), which, in turn, controls the remainder of the system and updates the stimulator outputs. The system can provide a high output current of up to 25.4 mA and a high output voltage of up to 18 V, with the current per electrode being software-limited to a maximum of 6 mA. The stimulation pulse width ranges between 10 μ s and 1280 μ s and the pulse repetition rate between 0.15 Hz and 7 kHz.

Table 3.1 summarises these characteristics of the system in comparison with other existing experimental setups aiming at locomotion recovery or targeting the DRG. The number of independently programmable channels refers to the option of programming the stimulation parameters individually for every channel. Out of a total of 16, the current configuration allows for control of 8 channels, to be used in order to stimulate the DRG bilaterally (on both sides of the SC) on 4 spinal cord levels, using 2 channels (2 leads) for each level. The number of independently addressable electrode points refers to the possibility of setting each electrode as anode, cathode or neutral (no current flow), without changing the physical connections to the leads. Out of a total of 32 electrode points, 16 are currently independently addressable, which can be expanded to 32 by adding a demultiplexer to the topology. These characteristics allow for the versatility that is required to study the effects of multi-site DRG stimulation for locomotion recovery.

3.2.3. SAFETY CONSIDERATIONS & SYSTEM VALIDATION

The safety requirements that need to be met differ significantly for preclinical (animal) and clinical (human) research, which often dictates the need for clinical research to rely on previously tested and approved components. Clinical research focuses, to a large extent, on the safety, comfort, and well-being of the patients participating in the studies. In the following paragraphs, we discuss how to consider the above requirements when designing a system for clinical research.

To begin with, we consider the type of clinical studies in which the device will be used, in terms of duration and mode of application. In this case, the envisioned studies will be conducted in-hospital and for a short period of time, as part of a larger chronic trial. Following this decision, the hardware items that will be used in the studies need to be identified. For our application, these are the CE-marked DRG leads and the developed stimulator prototype. As the DRG leads are already CE-marked, all further safety considerations and device testing are conducted with regards to the stimulator prototype and the system as a whole, grouped into risk assessments regarding (1) risk of infection and (2) the electrical functionality of the device, for the safety of both the patient and the medical personnel involved.

(1) Infection-related risks: It is important to ensure that no non-sterile parts are in direct contact with the patient to eliminate risks of infection or injury. In our proposed prototype, the only parts in direct contact with neuronal tissue are the already CE-marked DRG leads, which are kept sterile. The stimulator is in physical contact with the stimulating DRG lead only through an externalised, non-sterile lead extension. Before a chronic lead and device implantation, the externalised extension will be removed.

Table 3.1: Comparison of neuromodulation devices.

	This work	[9] ^a	[19]	[7]	[20]
Goal	Restoring Locomotion	Restoring Locomotion	Somatosensory Neuroprostheses	Restoring Locomotion	Pain Relief
Stimulation Target ^b	DRG	DRG	DRG	SC	SC
Preclinical vs. Clinical	Under review for Clinical	Clinical	Preclinical	Clinical	Clinical
No. of independently program. channels in total / for bilateral control	16/8	1/4	1/1	1/1	32
No. of electrode points in total / independently addressable	32/16	16/16	32/32	16/16	32
Levels of bilateral stimulation ^c	4	2	1	1	2
Stimulation parameters (current amplitude, frequency, pulse width)	0 - 25.4 mA ^d 0.15 Hz - 7 kHz 10 - 1280 μ s	0 - 6 mA 4 - 80 Hz 40 - 1000 μ s	0 - 1.5 mA 0 - 1 kHz 100 μ s - 50 ms	0 - 16 mA 2 - 1200 Hz 60 - 1000 μ s	0 - 25.5 mA 0 - 1.2 kHz 20 - 1000 μ s

^aThe system used in [9] is originally intended for pain relief. However, it is the only system in the literature used for restoring locomotion when stimulating the DRG.

^bAll systems use Current-Controlled Stimulation (constant current pulses).

^cFor use in DRG stimulation, based on the number of leads that can be connected to the IPG.

^dThe stimulator is capable of delivering 25.4mA in total for a parallel electrode configuration, if required; however, a delivery of max. 6mA per electrode will be limited by the software of the device.

(2) Electrical-functionality-related risks: The safety of the patient as well as of the medical personnel must be ensured in case of a single-fault failure. To establish this, parameters related to powering the device, protection from direct current (DC) leakage, and ensuring safe operation are considered.

In this implementation, the device is powered from the mains for a constant and reliable supply, while a medical AC/DC adapter (MDS-030AAC05, Delta Electronics) is chosen for proper protection and isolation of the device. The adapter is suitable for type BF (body float) applications, namely for applications that have conductive contact with the patient, as it exhibits a low touch current. This means that any current leakage paths that might be in contact with the patient or operator will not exceed a specific threshold. A double Means Of Patient Protection (MOPP) isolation provides a double layer of insulation to protect the patient from any electrically charged equipment that might come in contact with the device, and an IP22 ingress protection rating protects the adapter against the insertion of fingers and maintains its safety even when exposed to dripping water.

In the event of a device fault, any DC that might leak through the electrode can cause great damage to the neural tissue. To prevent this, medical-grade coupling capacitors (tantalum capacitors, $10\mu\text{F}$) are placed in series with the stimulating electrodes, for both the anodic and the cathodic paths of the stimulating current. These capacitors are specifically designed for use in non-critical medical applications, exhibiting DC leakage levels that are significantly lower than commercial solid tantalum capacitors.

The device is enclosed in a polymer casing, guarding its electronic components from the outside environment and providing electrical isolation between the device and its users. Any openings in the casing, made to allow for a connection to the stimulating leads or the powering adapter, are secured with rubber cable grommets to reinforce the hole through which the cables pass and to protect the cable from any sharp edges and vibrations. Furthermore, the rubber grommets prevent the cable from sliding due to friction.

To verify its safe use, the stimulator prototype underwent a safety evaluation. For that purpose, the device was tested using the Abbott® DRG leads submerged in a phosphate-buffered saline (PBS) solution (0.14 M NaCl, 2.7 mM KCl, 10 mM phosphate buffer, with a pH value of 7.4 ± 0.05) to emulate the environment of the inner body, as well as with a chicken breast phantom model. The measurements were conducted with the 3-Series Mixed Domain Oscilloscope (MDO34) by Tektronix®. The setup for the measurements can be seen in Fig. 3.3. Fig. 3.4 illustrates the various stimulation waveforms and patterns that the proposed system can deliver.

To demonstrate the proper and safe function of the stimulator, the voltage between the anode and the cathode of the system was observed (shown in Fig. 3.5) [13]. The voltage drop of 1.1 V at the beginning of the stimulus pulse is a product of the resistive behaviour of the electrolyte, while the capacitive nature of the stimulating electrodes results in an almost linear change of the measured voltage during both phases of the biphasic pulse. The potential difference between points 1 and 2 of Fig. 3.5 should be in the range of a specific potential, known as the water window, outside which electrolysis occurs. This potential is relative to the electrode material,

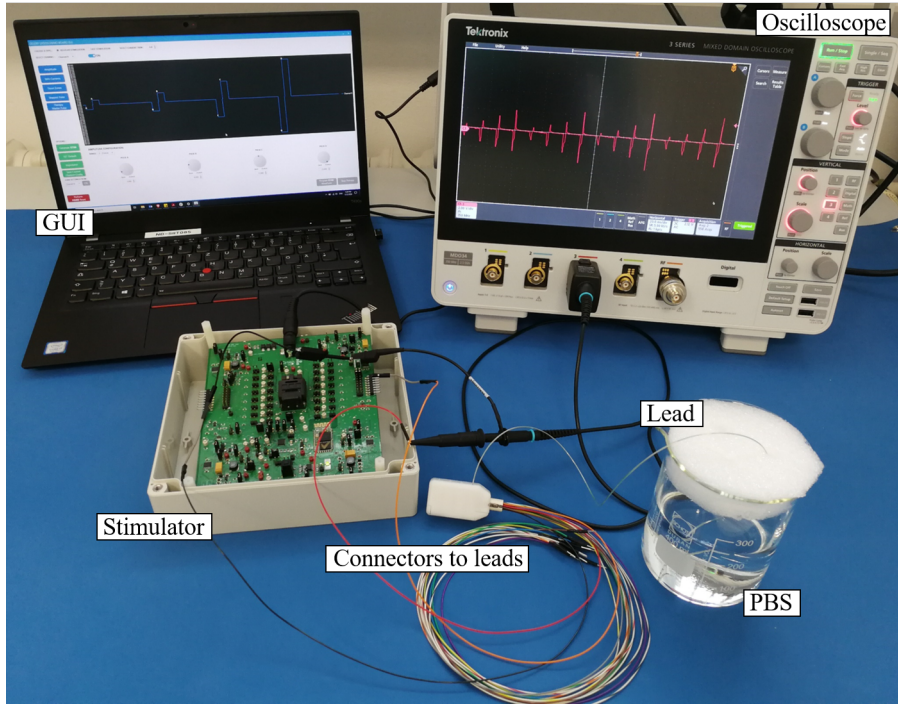


Figure 3.3: Measurement setup used for the safety evaluation of the stimulator prototype. The DRG leads are connected to the stimulator on one end and submerged in a PBS solution on the other end. The stimulating sequences are programmed through a GUI on a laptop, and the output signals are measured with an oscilloscope.

in this case platinum-iridium (PtIr). Here, it is measured at -0.6V at point 1 and 0.25V at point 2 (falling to 0.12V after only $100\mu\text{s}$), which falls inside the suggested water window for Pt and PtIr electrodes, at $\phi > -830\text{mV}$ and $\phi < 1230\text{mV}$ respectively [21]. Finally, the interpulse potential (point 3 on Fig. 3.5), an effect that builds up after a number of biphasic pulses, should remain close to zero so that it will not allow for any harmful electrochemical reactions. Here, it is measured at 70mV , which we expect is low enough as to not harm the stimulated tissue [22].

Another parameter that is considered regarding the safety of the stimulator is the stimulation parameter k as described by the Shannon equation, a dimensionless parameter expressing the relation between the charge density (charge per surface area) and the charge per phase of a stimulation pulse. This parameter is more representative of microelectrodes but tends to overestimate or underestimate the safety limits for microelectrodes, as those used in this system [23]. In any case, the maximum charge density to be delivered at 6mA , $D = 30.5\mu\text{C}/\text{cm}^2$, falls in the accepted levels for FDA-approved devices [23].

Finally, to determine if there is any tissue overheating at the stimulating leads, a thermal analysis was conducted with the E60 Thermal Imaging Camera of Flir.

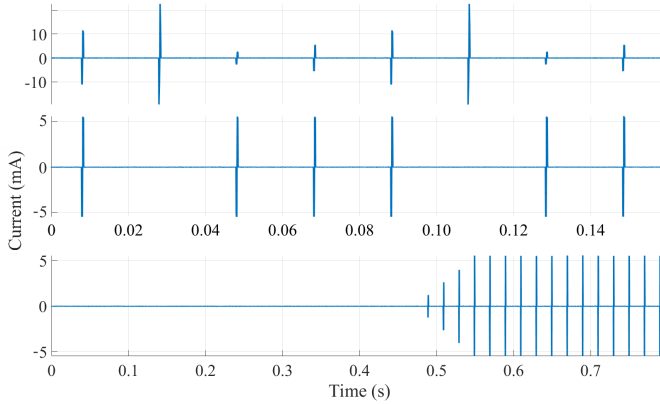


Figure 3.4: Delivered current, as measured over a 511Ω resistor, when delivering 3/6/12/25mA to the load (**top graph**), when skipping a pulse in the stimulation sequence (**middle graph**), when ramping up the stimulation sequence (**bottom graph**), all at a 48Hz frequency.

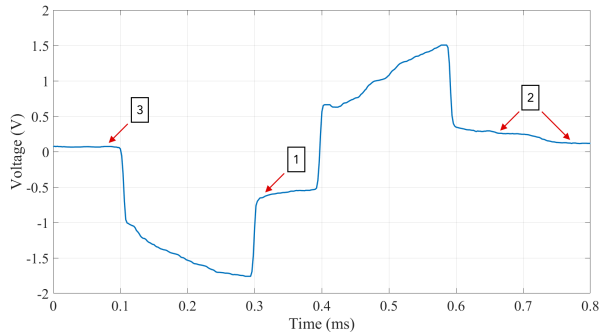


Figure 3.5: Measured voltage between the anode and the cathode of the system, when delivering 6mA to the load at a 48Hz frequency.

The temperature at the leads inserted in the chicken breast phantom model was compared before and after 30 minutes of continuous stimulation, at the highest possible current level of 25.4 mA, a frequency of 350 Hz and a pulse width of 1280 μ s. The results of the thermal measurements are presented in Fig. 3.6, demonstrating no significant changes in the temperature at the lead. The temperature rose from 14.7°C to 16.4°C, with the temperature at the tissue area directly surrounding the lead being at 15.9°C, overall remaining under the 2°C-increase limit suggested by the FDA. It should, however, be noted that these measurements were performed ex vivo in an environment with uncontrolled air flow and humidity, hence are not fully representative of an in vivo scenario.

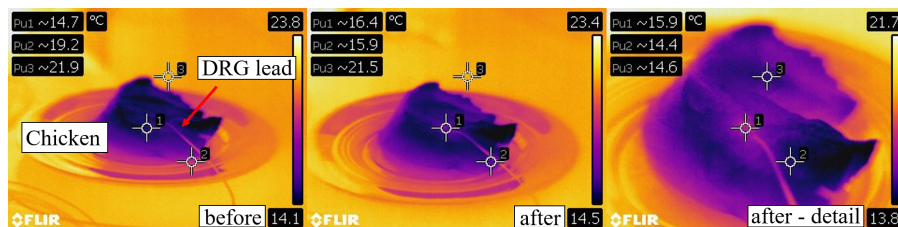


Figure 3.6: Temperature change measured at the DRG lead in a chicken tissue phantom model, before and after 30 minutes of continuous stimulation (pulse characteristics: amplitude of 25.4 mA, pulse width of 1280 μ s, frequency of 350 Hz).

3.3. STAND-ALONE BROAD FREQUENCY RANGE CHARGE BALANCING SYSTEM

In the design of neural stimulators, it has been customary to include features that aim to balance the charge between the stimulation pulses. This aids in compensating for the offset voltage buildup that the electronic system sees at its output after the end of a stimulation phase as a result of charge accumulation, and is implemented as a means of increasing stimulation safety and avoiding harmful electrochemical reactions at the electrode-tissue interface (ETI). This approach, unfortunately, cannot guarantee safety, as any electrode voltage offset should ideally be minimised versus a non-polarisable reference electrode, e.g. a silver/silver chloride (Ag/AgCl) electrode. However, in the absence of such reference electrodes in vivo, the best practice for the field has been to either accurately charge-balance the two phases of each stimulation pulse, or to focus on minimising any offset between the output terminals of the system or the system ground.

Most commercially available stimulators include a passive charge balancing (CB) approach, which receives no feedback from the electrode site regarding any remaining offset voltage that can lead to such harmful reactions. An example of a conventional CB method is electrode shorting, where the stimulating electrodes are shorted to allow for discharging between the biphasic pulses [13]. This method, however, can be insufficient, especially for the high pulse repetition rate (PRR) of kilohertz frequency alternating current (KHFAC) signals [24], as the discharge time may be too short. The most commonly used CB measure is to place a DC blocking capacitor between the stimulator and each stimulating electrode, thus establishing the behaviour of a high-pass filter (HPF) [25]. However, [25] shows that such a DC blocking capacitor can introduce an additional offset voltage that is difficult to control by the stimulator.

Active CB approaches include a feedback pathway that provides information about the offset voltage at the electrode site. Most approaches focus on stimulation patterns used to excite neural activity and, therefore, on frequencies below 500 Hz. These can be divided into CB methods that modify the stimulation pattern in timing [26] or amplitude [27], [28], when there is access to its programmability, and CB

methods that inject charge in addition to the stimulation pulse [29]. A popular method of charge injection is pulse insertion, as described in [30]. If the measured offset voltage is not within the given safety limits, predefined charge packages are applied until the voltage is again within the safety window. An alternative charge injection approach is the offset compensation (OC) technique [22]. Here, a constant offset current is applied either permanently or only during a dedicated phase to minimise the electrode offset voltage [22].

The stand-alone CB system developed here can be used as an extension for any stimulator. The system is compatible with a broad range of frequencies and is particularly beneficial for the more demanding PRRs of the KHFAC applications. It operates independently of the stimulator timing by continuously sensing the offset voltage and applying a corrective current to the electrode using the OC technique. To ensure its stand-alone capability, the system is battery-powered and includes a safety and start-up circuit. The device is built using commercially available components, thus ensuring its reproducibility and ease of access. Electrical measurements verified the functionality of the circuit, demonstrating a residual offset of only 0.7 mV for 1 V biphasic pulses at 50 kHz. When tested for 20 kHz biphasic pulse at a 5 V amplitude, the offset was measured at 11.6 mV, which is still within the (commonly used) ± 50 mV safety window.

3.3.1. SYSTEM-LEVEL DESIGN

The proposed system consists of a core circuit, divided into a measurement part and a charge injection part (Fig. 3.7a). The measurement part incorporates a voltage follower, an integrator and an amplifier. The electrode offset voltage is forwarded to the integrator, where it is compared to a reference - here, the ground potential. The difference between the electrode voltage and the reference is integrated and converted into a current through a voltage-controlled current source (VCCS), which represents the charge injection part of the system. This current is added to the stimulator current, the sum of which is the final current applied to the electrode. The system is powered through a rechargeable 3.7 V lithium polymer battery, which can be recharged through a USB connection to a laptop or PC (Fig. 3.7b). A safety and start-up circuit ensure the reliable operation of the system.

Charge Balancing Circuit

To design a system capable of charge balancing for a broad frequency range, the focus is set on the short duration between pulses (interpulse delay) for KHFAC stimulation and the high-frequency components of the signals applied during neuromodulation. The continuous measurement of the electrode offset voltage and the OC scheme allow independence from the stimulator timing and the duration of the interpulse delay. Fig. 3.8 illustrates the utilised OC method at the example of a biphasic stimulation pulse with a 20% amplitude mismatch between the two phases. Fig. 3.9 presents an overview of the system's core circuit elements.

Measuring the electrode offset voltage is an important first step within the feedback loop of the proposed CB system. Any mismatch between the actual and

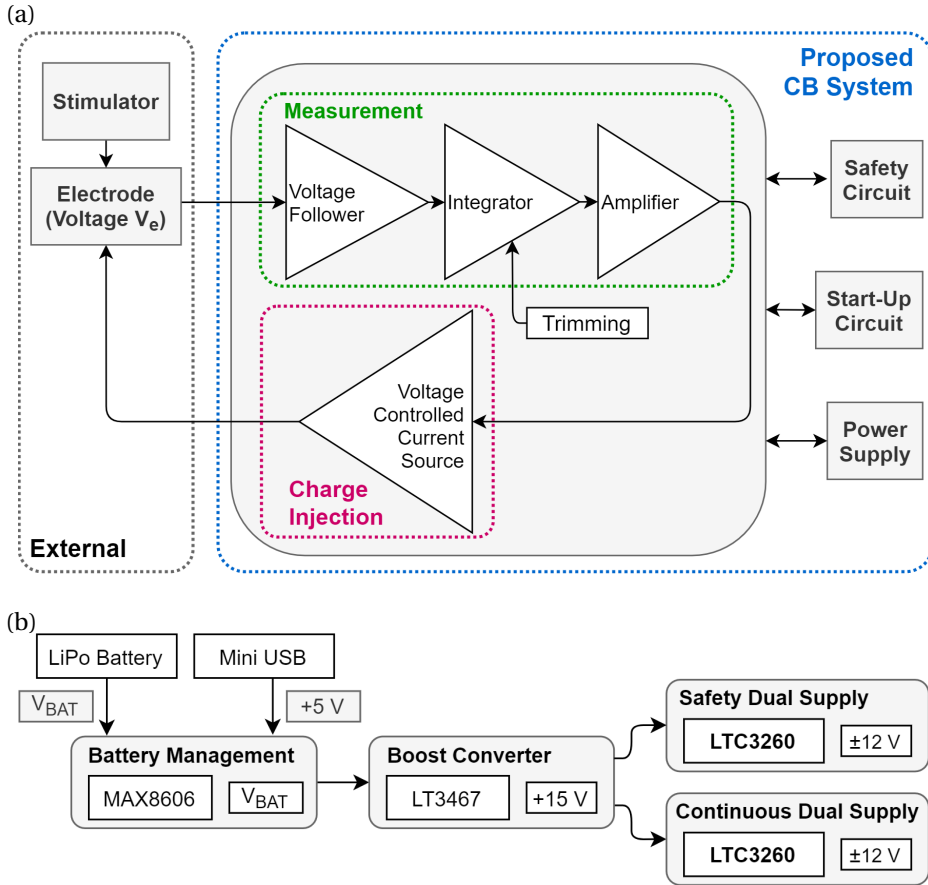


Figure 3.7: (a) Block diagram of the complete proposed CB system. The voltage follower output, which provides the electrode offset voltage, is forwarded to an integrator. This integrator compares the value to a reference, integrates it, and then forwards the result to an amplifier. This output is eventually used to drive a VCCS. (b) Diagram of the external supply and the supply levels within the system.

the measured offset would lead to an error in the signal used for offset correction, thus resulting in an accumulating offset voltage at the electrode. A simple voltage follower configuration using an operational amplifier (OpAmp) provides a copy of the electrode voltage to the subsequent circuitry and offers a high input impedance. The electrode voltage is measured across the working and counter electrodes with reference to ground. A sufficiently high input impedance is required, compared to the impedance of the electrode connecting to the system, to prevent any stimulation current from leaking into the voltage follower input and potentially disrupting the stimulation pulse and falsifying the measurement result. Furthermore, sufficient slew

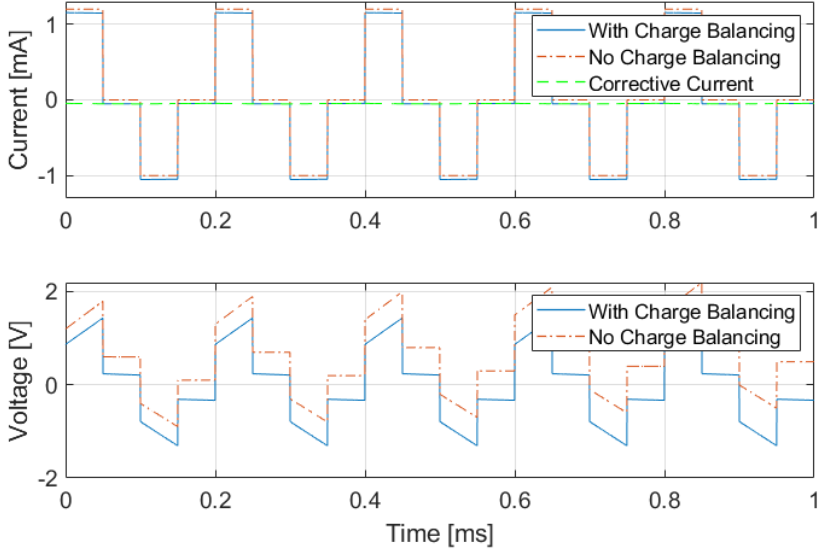


Figure 3.8: Simulation exhibiting the outcome of using the OC method for CB when introducing a 20% mismatch between the amplitudes of the anodic and cathodic phases. The values used for the electrode model are $R_S = 1\text{ k}\Omega$ for the spreading resistance, $R_F = 1\text{ M}\Omega$ for the faradaic resistance and $C_{DL} = 100\text{ nF}$ for the double layer capacitance. **top graph:** Balanced (in blue) and unbalanced (in red) stimulation currents, with the corresponding corrective current (in green), as a function of time. **bottom graph:** Voltage measured at the electrode site for balanced (in blue) and unbalanced (pulse) pulse patterns as a function of time. When the 20% amplitude mismatch is not corrected, the offset voltage at the electrode site continues to increase.

rate (SR) is required for the OpAmp to ensure linearity for the stimulation signal's frequency range.

While [31] uses a low-pass filter (LPF) to integrate the electrode voltage over several stimulation periods and continuously determine the offset voltage, the CB system proposed here follows the recommendation of [32, pp. 26–27], suggesting that integration is more accurate when an active integrator configuration with an OpAmp is used. The integrator has a time constant defined by R_{int} and C_{int} , which needs to be larger than the period of the biphasic pulse. For nerve conduction block stimulation frequencies between 1 kHz and 20 kHz, a time constant of 10 ms results in 10 and 2000 integrated periods, respectively.

A buffered trimming circuit is connected to the non-inverting input of the integrator's OpAmp. A trimming circuit is typically used to solve offset problems. Furthermore, it allows the user to add a defined offset to the electrode voltage, similar to the implementation in [31]. As [33] suggests, an offset voltage of up to several hundred millivolts results in better electrode performance for some electrode materials, such as Iridium Oxide or PEDOT, as they improve their charge injection

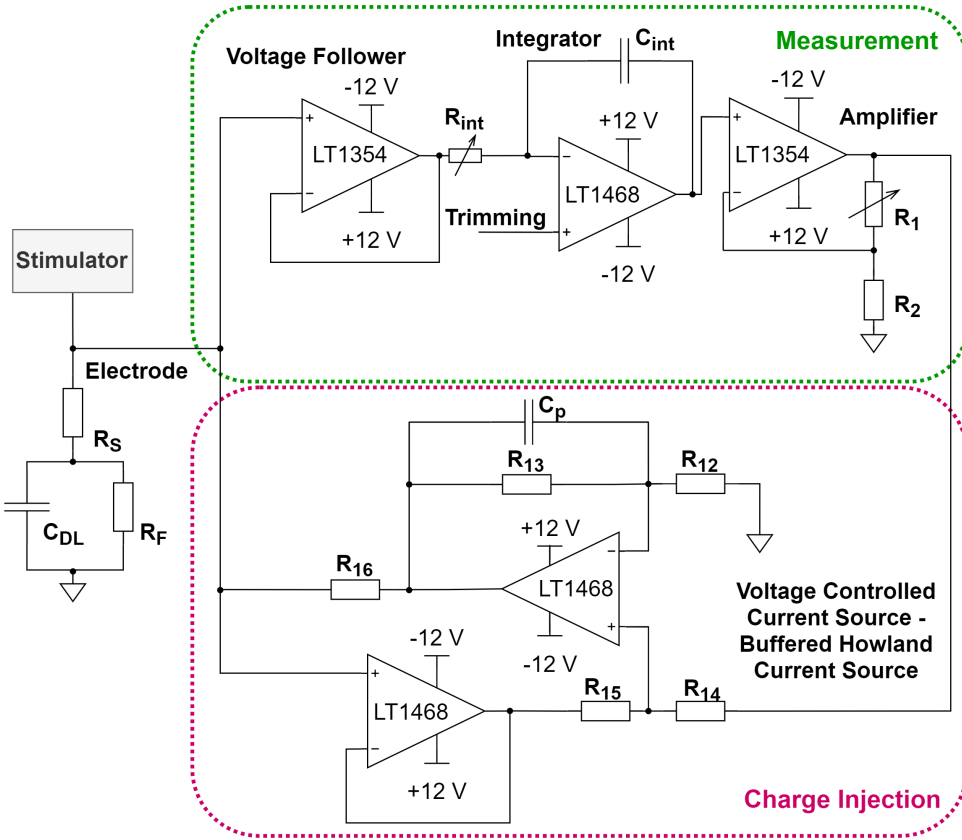


Figure 3.9: Schematic of the system's core circuit consisting of five OpAmps. The electrode model represents one electrode consisting of the spreading resistance R_s , the faradaic resistance R_F and the double layer capacitance C_{DL} . $R_{int} = 1\ \Omega - 100\ \text{k}\Omega$, $C_{int} = 1\ \mu\text{F}$, $R_1 = 1\ \Omega - 100\ \text{k}\Omega$, $R_2 = 1\ \text{k}\Omega$, $R_{12}-R_{16} = 10\ \text{k}\Omega$, $C_p = 5\ \text{pF}$.

capacity when biased. The integrator is followed by a non-inverting amplifier. The amplification of the integrator output results in a faster settling of the circuit by adding a gain to the feedback. A potentiometer (R_1) permits the user to adjust this gain.

The amplified integrator output drives a VCCS connected to the electrode. A commonly used VCCS is the howland current source (HCS). One issue that is often overlooked when using the HCS in stimulators, as in [31], is the low output impedance at high frequencies. The buffered HCS used here (Fig. 3.9) improves the output impedance by zeroing the feedback current through R_{15} . Equally important is finding matching resistors for $R_{12}-R_{15}$, as a mismatch would result in lower output impedance. Therefore, a resistor network is used. Furthermore, the frequency-dependent gain of the OpAmps, following from the component's GBW, results in a decreasing output impedance of the HCS with increasing frequency, thus

requiring an OpAmp with a high GBW. In this HCS configuration, the resistor R_{16} at the output defines the ratio of the input voltage to the output current. A capacitor C_p is added to the feedback path of the OpAmp to increase its stability.

Safety Circuit

A safety circuit is implemented to handle errors due to voltage follower saturation at high input voltages. Turning off the power supply is a straightforward way of turning off the complete system. Therefore, the power management system includes its dual-supply ASIC twice: one that is continuously operated and one that is controlled by the safety circuit. When the safety dual-supply ASIC is disabled by the safety circuit, the HCS, the amplifier, and the integrator are turned off to ensure that no offset current is applied to the ETI unintentionally.

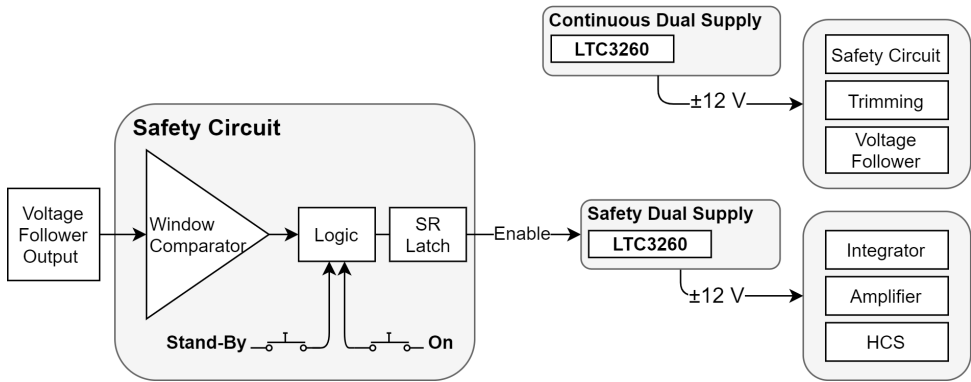


Figure 3.10: Schematic description of the safety circuit to prevent system malfunction in case of saturation and the concept of the split power supply. The safety circuit compares the output voltage of the voltage follower to a reference window. A logic circuit, which also takes two buttons as inputs, evaluates if the circuit should be switched on or off.

Start-Up Circuit

Two issues arise when starting up the circuit. First, the safety dual supply does not provide the positive and negative voltages with equal SRs. This creates an imbalance in the system, resulting in an incorrect output current at the HCS during start-up. Second, charge is stored in the integrator's capacitor due to offset and bias currents [32, pp. 230–231], causing an additional error, where overshoot oscillations may occur at start-up. To address this, analog switches short-circuit this capacitor and connect the integrator's OpAmp input to ground to ensure its discharge until the system is powered up. In addition, a reed relay connects the system's output and the stimulating electrode to ground, until the system is adequately powered up. The analog switches and the reed relay are normally closed (NC) and open with the signal generated by the start-up circuit. This signal is generated by a comparator that compares the voltage level of the safety dual supply to that of the continuous

dual supply, with the comparator output switching from low to high as soon as the safety dual supply reaches the level of the continuous dual supply.

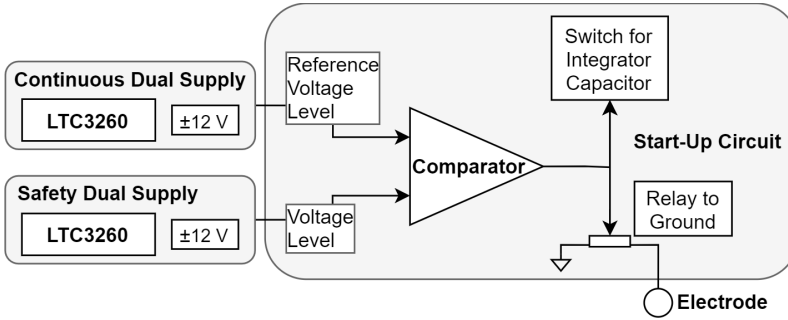
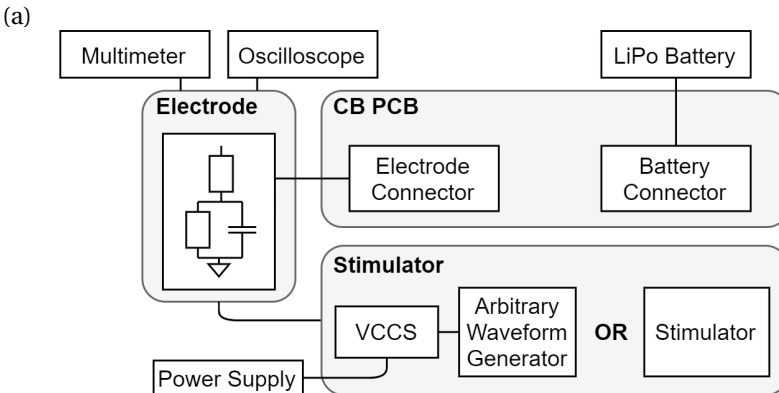


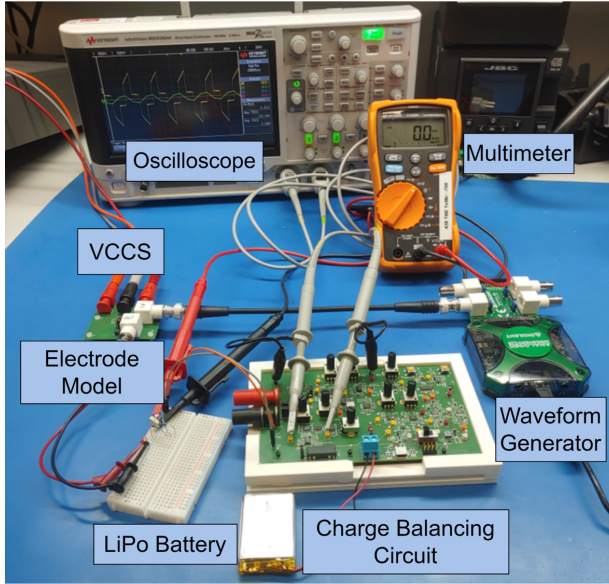
Figure 3.11: Schematic of the start-up circuit and its connections. A comparator evaluates the voltage levels of the dual safety supply against reference voltages, supplied by the continuous dual supply. The output signal stirs the reed-relay, which shorts the electrode to ground and the analog switches to discharge the integrator's capacitor.

3.3.2. SYSTEM VALIDATION & MEASUREMENT RESULTS

The validation of the CB system and the additional safety and start-up circuit requires a setup that includes an arbitrary current source to emulate the stimulation signal, an electrode model, and additional measurement equipment, as shown in Fig. 3.12a. An arbitrary function generator (Analog Discovery 2) followed by a VCCS allows for an adjustable simulation of pulse mismatches or added offsets to test the efficacy of the developed CB system. The VCCS used for this purpose is the same HCS as used in the CB system, with a transconductance of 1 mS, resulting in 1 mA output current for 1 V input voltage. The DC voltage setting on the multimeter



(b)



(c)

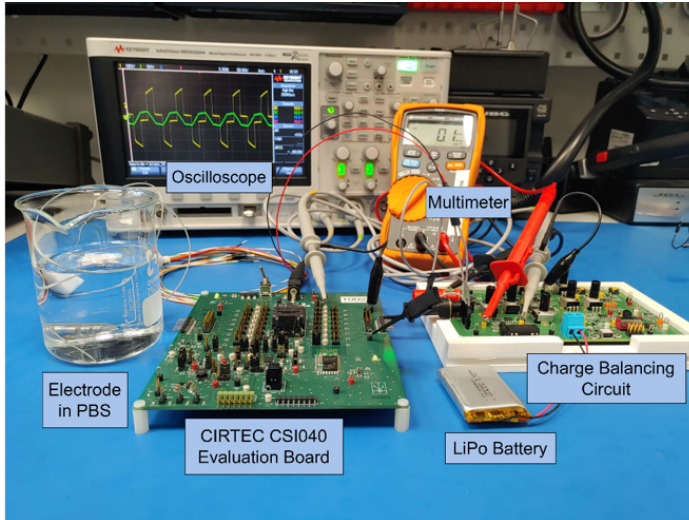


Figure 3.12: (a) Schematic representation of the test setup pointing out the connections between all used instruments. (b) Test setup with the arbitrary function generator (Analog Discovery 2) followed by the VCCS and the linear ETI model. (c) Test setup with the CSI040 neurostimulator ASIC and the CE-marked DRG leads from Abbott®.

(Keysight U1233A) measures the offset of the stimulation pulses. An oscilloscope (InfiniiVision MSOX2024A) measures all time-continuous signals.

A linear electrode model consisting of two resistors and one capacitor allows for

controlled testing with $R_S = 1\text{ k}\Omega$, $R_F = 1\text{ M}\Omega$, and $C_{DL} = 100\text{ nF}$, resulting in a well-defined impedance (Fig. 3.12b). Finally, the system is tested together with a commercially available neurostimulator ASIC, the CSI040 by Cirtec Medical, and the CE-marked DRG leads from Abbott[®] (Proclaim[™] DRG) (Fig. 3.12c).

A series of measurements is conducted to show the functionality of the utilised OC scheme for a linear ETI model. First, a constant offset is added to the emulated stimulator current. As Fig. 3.13 shows, the stimulator current, which is a biphasic pulse with 1 mA amplitude and a frequency of 5 kHz, is shifted by $200\text{ }\mu\text{A}$. The corrective current has the expected value of $-200\text{ }\mu\text{A}$, resulting in the charge-balanced electrode current.

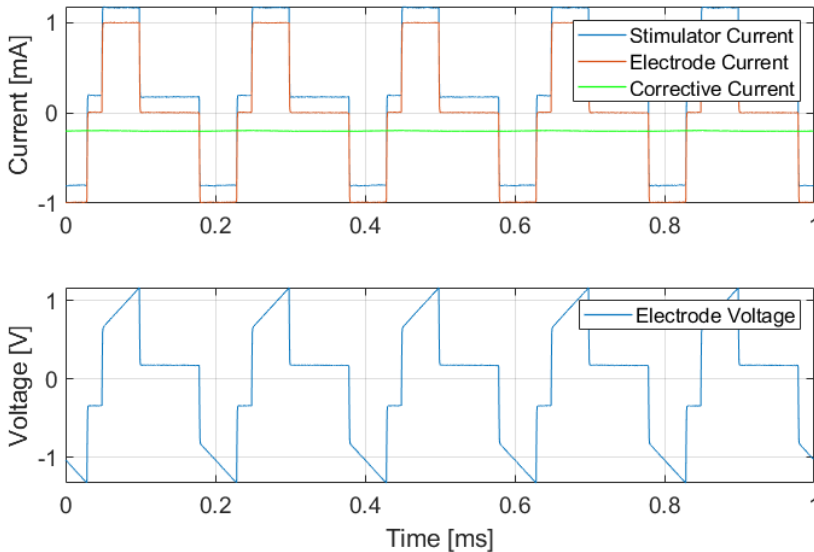


Figure 3.13: **top graph:** Stimulator, electrode, and corrective current as a function of time with the corrective current adapting to the offset, so that the current through the electrode, which is the sum of the stimulator and corrective current, does not have an offset. **bottom graph:** Charge-balanced electrode voltage as a function of time. Measurements conducted with an ETI model.

A different scenario that causes a charge imbalance is a mismatch between the cathodic and anodic phases of a stimulation pulse. To evaluate the capabilities of the CB system, a mismatch of 10% is applied to the biphasic pulse. The electrode offset voltage is measured for different pulse frequencies and amplitudes, as shown in Fig. 3.14. The system maintains the offset voltage below 0.7 mV for a pulse amplitude of 1 mA current, resulting in approx. 1 V for up to 50 kHz. For a voltage amplitude of 5 V and a frequency of 20 kHz, the offset is at 11.6 mV . The offset voltage measurements result in the same values for a signal with and without a 10% mismatch, indicating the efficacy of the developed CB system.

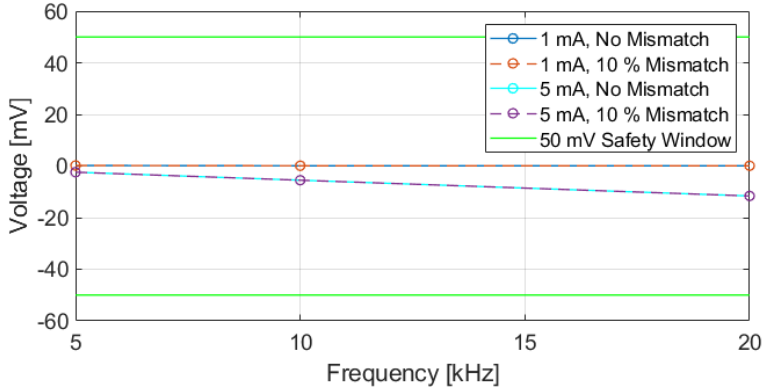


Figure 3.14: Electrode offset voltage as a function of frequency depending on the amplitude and frequency of the applied pulses. Measurements conducted with the linear ETI model.

The time constant of the feedback loop influences the shape of the corrective current and the start-up behaviour, as shown in Fig. 3.15. Again, an offset of $200\mu\text{A}$ is added to the VCCS signal. Now the feedback loop time constant, which consists of the HCS's transconductance (0.1 mS), the amplifier's gain (93 V/V), and the integrator's time constant, is varied by setting different integrator time constants. The middle graph of Fig. 3.15 shows how the corrective current changes accordingly: a smaller time constant increases its peak-to-peak value, influencing the electrode voltage shape.

The feedback loop's time constant furthermore influences the initial settling of the corrective current at start-up (Fig. 3.15, bottom graph). A reduced time constant results in a faster settling behaviour and fewer overshoots. Therefore, the time constant should be adjusted to the application's requirements. Adapting the time constant also allows for extending the frequency range over which the system can be used. With an adapted time constant, the system has been tested for frequencies as low as 20 Hz and as high as 50 kHz .

Finally, to show the functionality of the utilised OC scheme for a non-linear ETI model, the system is tested with the CE-marked DRG leads from Abbott[®] submerged in a PBS solution. Fig. 3.16 shows the electrode voltage measured across the working and counter electrode at the electrode site, with the respective corrective current measured and displayed as a voltage, to highlight the direct correlation of the two.

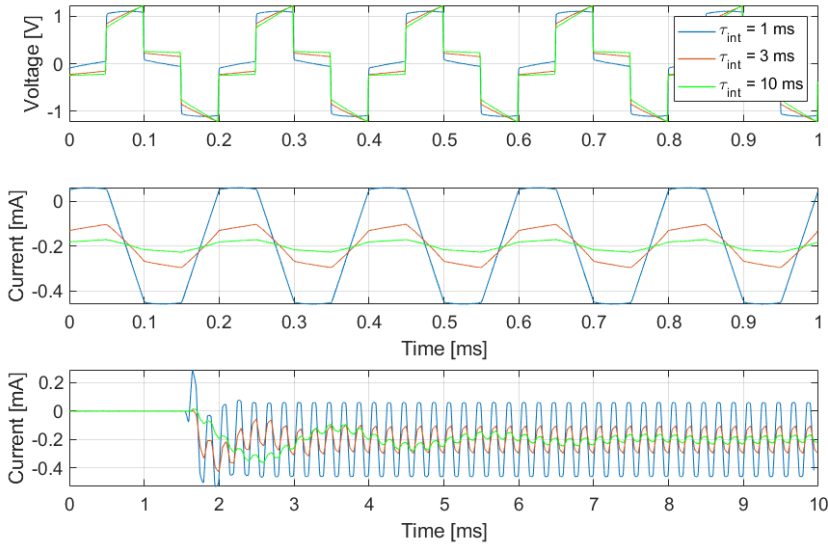


Figure 3.15: *Electrode voltage (top graph), amplitude of the corrective current (middle graph), and corrective current during the start-up phase (bottom graph) as a function of time for various feedback loop time constants. Measurements conducted with an ETI model.*

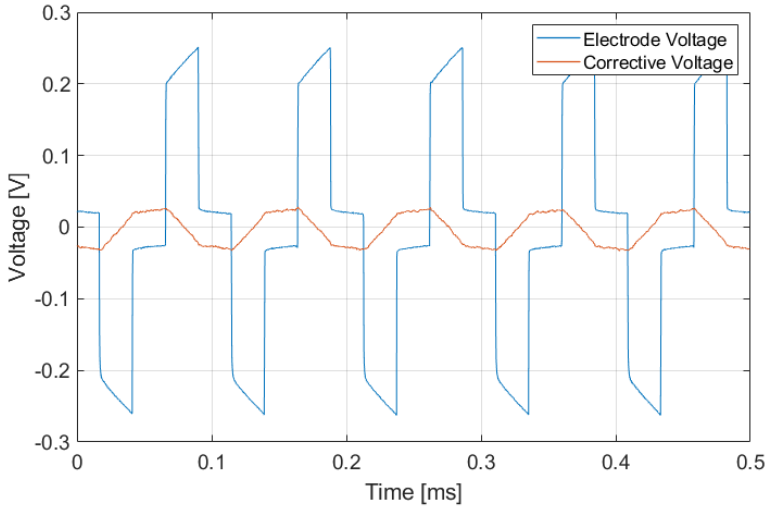


Figure 3.16: *Electrode voltage and applied corrective current, measured and displayed as a voltage, as a function of time. Measurement conducted with an electrode submerged in a PBS solution.*

3.4. APPLICATION PROCEDURE FOR RECEIVING ETHICS COMMITTEE APPROVAL

Prior to its inclusion in any clinical trial, a medical device has to be evaluated and approved by the responsible local Ethics Committee. In the case of the DRG stimulator prototype, the final design of the prototype system would need to be approved by the Erasmus Medical Centre Medical Ethics Review Committee (METC), as the partner that would be conducting the clinical trials. For that purpose, the Investigational Medical Device Dossier (IMDD), a protocol containing all information on a non-CE marked device intended to be used in clinical trials, must be provided. According to the CCMO-website (the Dutch Central Committee on Research Involving Human Subjects) (www.ccmo.nl), this IMDD is based on Annex II (technical documentation) of the EU Medical Device Regulation (EU nr 2017/745). Amongst the requested information for the IMDD, researchers must provide an extensive device description (including design and manufacturing when relevant), a risk analysis, an Essential Requirements Checklist, including the requirements for the safety and performance of the device, and evidence of conformity to all other general requirements, such as biocompatibility, sterility, etc., when applicable. Unfortunately, due to unforeseen events (Covid-19 pandemic) and project limitations, the related clinical trials were postponed, and the documentation for the DRG stimulator was not submitted for approval. However, all necessary documentation has been prepared for submission and is available upon request.

3.5. CONCLUSION

The developed DRG stimulator prototype allows for a very versatile experimental protocol: high output current up to 25.4 mA and a high output voltage up to 18 V, stimulation pulse width ranges between 10 μ s and 1280 μ s and pulse repetition rates between 0.15 Hz and 7 kHz. It furthermore features a very large number of independent stimulation channels (8 channels for bilateral stimulation using 2 channels (2 leads) for each level of the SC), making it suitable for clinical use in locomotion recovery and locomotion control applications.

The stimulator prototype was complemented by the stand-alone CB system utilising the OC technique. The developed system allows for a stimulator-independent operation and can operate as a plug-in for any existing stimulator. It is furthermore suited for both neural activity excitation and inhibition applications. The system achieves a precise CB for signals in a broad frequency range up to 50 kHz, with measured offset voltages as low as 0.7 mV.

The characteristics of both systems, and especially of the DRG stimulator prototype, were tailored to ensure their suitability for use in a clinical trial setting. Hence, emphasis was placed on safety, configurability and user-friendliness of the devices. The development process and design considerations for the DRG stimulator prototype, being a device interfacing (indirectly) with neuronal tissue, can serve as a guide for similar attempts. The reproducibility of both devices, given the

use of commercially available components, along with the introduced list of safety considerations, may facilitate their application in related experimental settings.

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ULTRASONICALLY POWERED NEUROMODULATION PLATFORM INTENDED FOR SPATIALLY AND DIRECTIONALLY SELECTIVE ELECTRICAL STIMULATION

*There are no ideas – there are only people that carry ideas around –
and ideas get their stature from the people that carry them.*

Nikos Kazantzakis

Parts of this chapter have been published as a preprint on BioArxiv [1]. These parts are a verbatim copy of this article, with minor changes to comply with the format of this thesis. Reprinted, with permission, from [1]. All research data and code supporting the findings described in this chapter are available in 4TU.ResearchData at <https://doi.org/10.4121/6d7aa971-7e51-49ba-b1f8-2d75f64d3e90>.

4.1. INTRODUCTION

Vagus nerve stimulation (VNS) has demonstrated great potential in treating a number of neurological and psychiatric disorders, leading to its gradual FDA approval for the treatment of epilepsy, treatment-resistant depression, and post-stroke motor rehabilitation since 1997 [2–4]. Nonetheless, the full potential of the therapeutic effects of VNS is still being identified, with promising recent advances in the treatment of autoimmune diseases such as rheumatoid arthritis and Crohn's disease [5], chronic pain [6] and cardiovascular disease [7], due to its anti-inflammatory effects.

Despite its therapeutic potential, the common practice of stimulating the whole vagus nerve and thus the lack of target selectivity during VNS is a cause of unwanted side effects, including bradycardia, cough, hoarseness, and headache [8–10]. Recent studies have shown that such side effects can be eliminated by targeting only the specific area of the nerve that includes the fibres of interest, thus offering spatially selective VNS [11, 12]. This can be achieved by using multi-contact cuff electrodes, where the contacts can be individually chosen around the circumference of the vagus nerve [13, 14]. Optimising VNS through spatial selectivity can give the possibility to better understand the relation to and target specific innervated areas inside the body [15].

The selectivity of VNS when targeting efferent organs can be further enhanced by blocking the activation of the afferent pathways when stimulating the vagus nerve and, as a result, only activating the efferent ones. This can be achieved through the application of pulses in the kilohertz domain (kilohertz frequency alternating current (KHFAC)), which has previously been demonstrated to achieve a safe and quickly reversible blocking of the nerve activity [16]. Inhibiting the activation of the afferent pathways through KHFAC leads to a temporary virtual vagotomy (transection of the vagus nerve) and, thus, directional stimulation selectivity, offering many advantages compared to the equivalent irreversible procedure [17].

Given the need to continuously explore the treatment possibilities that VNS has to offer, we developed a neuromodulation platform suitable for investigating the potential of VNS in preclinical and clinical settings. The platform is built entirely of commercially available components, making it accessible and reproducible by other research labs to serve as an experimental tool in a variety of applications [18]. It is intended for both neural activity excitation and inhibition and can be powered wirelessly through ultrasound (US), using the same signal for powering and stimulation.

Our proposed system has an output stage that supports a connection to 8 electrodes, two for the purpose of neural activity inhibition and six for excitation. By providing the capability to inhibit the propagation of action potentials along the nerve, while simultaneously exciting the nerve at a different location, we can achieve directional selectivity. Furthermore, each of the six excitatory electrodes can be individually selected and controlled, allowing the manipulation of the generated electric field and thus adding a degree of spatial selectivity of the activated area. The system delivers monophasic or biphasic electrical stimulation.

Due to the non-linear behaviour of the electrode-tissue interface (ETI) [19–21] and possible mismatches in the stimulation pulse phases due to hardware limitations and electronic component tolerances, charge can accumulate at the ETI, leading to the buildup of a residual DC voltage, which might cause irreversible electrochemical reactions, harming either the tissue or the electrode [22, 23]. A charge balancing scheme using a proportional-integral-derivative (PID) controller [24, 25] is implemented here to reduce the excess charge appearing at the stimulator output.

Aiming towards an eventual miniaturisation of the entire system, as envisioned in [26] and seen in Fig. 4.1, the platform is powered wirelessly through US. Using US has emerged as a promising method of powering fully implantable devices, providing an alternative to the commonly used inductive coupling that comes with higher tissue absorption rates, large coil sizes and smaller penetration depths. Previous studies have demonstrated successful power transfer to millimetre-scale implantable devices for peripheral nerve stimulation [27–29], highlighting its potential.

To increase the system's power efficiency, thereby reducing power dissipation and thus heat generation, the harvested signal used to power the system is also used for neural stimulation [30, 31]. The rectified sinusoid from the energy harvester is directly forwarded to the system's output stage and the stimulating electrodes, eliminating the need for an additional voltage or current source. Furthermore, the neuromodulation platform can be powered through a USB connection, or a battery for portability. The user can communicate with the platform through a graphical user interface (GUI) on a laptop or PC.

While each of these three essential building blocks (ultrasound-based wireless power transfer, multi-electrode spatially selective stimulation, active PID-based charge balancing) are valuable on their own, the key contribution of this work lies in their integration into a single, reproducible benchtop system built entirely from commercially available components. The resulting neuromodulation platform functions both as a versatile experimental tool for pre-clinical and clinical research, and as a prototype for identifying critical design parameters for the future miniaturisation of fully implantable, ultrasound-powered neurostimulators.

4.2. MATERIALS AND METHODS

A block diagram of the proposed neuromodulation platform is presented in Fig. 4.2a. The system consists of five main blocks. Acoustic energy is harvested, converted into the electrical domain and rectified within the Energy Harvesting block. This rectified signal can subsequently be used to power the platform and for stimulation at the output stage. An alternative power source is provided through a battery or a USB connection (also allowing for data transfer) and is part of the Power Supply & Data Transfer block. The Power Management block is responsible for all necessary power conversions to supply the system's components, while all logic operations are performed within the Control Unit block. Finally, the Output Stage enables the connection to the stimulation site. A detailed description of all individual blocks and components follows.

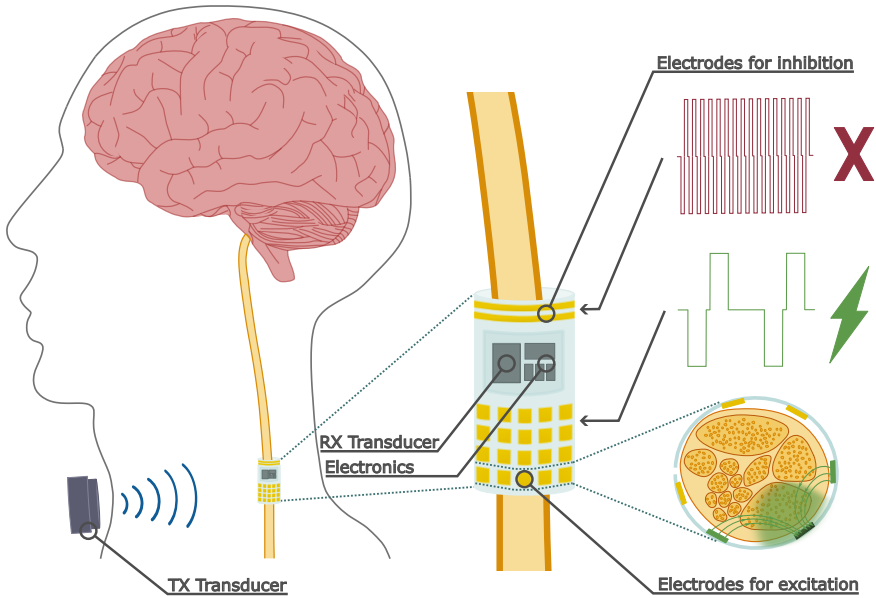


Figure 4.1: Concept of wireless battery-free neurostimulator implant. The miniaturised implant is powered wirelessly through ultrasound and uses the same harvested ultrasonic signal, converted into the electrical domain, for both powering and neural stimulation. The combination of direction-specific stimulation through KHFAC block and area-specific excitation through individually addressable electrodes allows for selective stimulation of the nerve's fascicles and fibres, depending on the targeted area. A benchtop neurostimulator platform is developed, which can be used to identify the most relevant parameters for VNS as well as the most effective and energy-efficient design for a miniaturised battery-free neural implant.

4.2.1. NEUROSTIMULATOR CIRCUIT HARDWARE

The neuromodulation platform can be powered through multiple sources. A USB connection to a laptop or PC provides a constant 5V supply to the system. When forwarded to the battery charge-management IC (MAX8606), it can recharge a 3.7V lithium polymer battery with 2000 mAh current capacity (RS Pro). Disconnecting from the USB supply and using the battery pack to provide the necessary power allows for a portable autonomous system that does not require any external connections. Finally, the platform can be powered wirelessly through US. The harvested acoustic energy is converted into the electrical domain through a receiving US transducer (RX). Depending on the transducer used as RX, a matching circuit can be included to maximise power transfer. The harvested signal is subsequently rectified, with four Schottky diodes (RB751CM-40) connected in a bridge circuit providing full-wave rectification.

The rectified voltage is forwarded to the upcoming power management blocks as well as the output stage of the system. A low-dropout (LDO) voltage regulator (TPS79730) regulates the rectified US signal to a constant 3V to power a

microcontroller unit, the STM32L562. Following the LDO, a step-up charge-pump DC-DC converter (MAX619) provides a regulated 5V to operate four single-pole, single-throw (SPST) analog switches (TMUX1112), each with four independently selectable channels, and three quad-channel operational amplifiers (OpAmps) (TLV9044). Both the TMUX1112 and the TLV9044 offer rail-to-rail input and output.

The same signal used for powering the platform is forwarded to the system's output for stimulation, thereby achieving voltage-controlled stimulation. This approach bypasses the requirement for an additional voltage or current source that is typically used in electrical stimulators and avoids unnecessary power conversions, thus implementing a more energy-efficient version of the system. When using the battery pack or the USB connection to supply the power, which is also useful for debugging and testing purposes, the system is decoupled from the wireless power supply. In this case, the US signal needed for stimulation can be emulated through a function generator.

The system's output stage supports a connection to eight electrodes, two for the purpose of neural activity inhibition and six for excitation. A choice can be made for either monophasic or biphasic stimulation. Monophasic stimulation offers the advantage of lower stimulation thresholds and higher spatial selectivity [32]; however, it compromises safety, which is why biphasic stimulation is preferred in recent stimulation protocols. Given the need for a biphasic pulse for neural stimulation, an H-bridge configuration at the output stage, using the TMUX1112 analog switches, allows for stimulation with both polarities while using one single power line - in this case, the full-wave rectified signal from the US transducer. This way, the two stimulation phases, cathodic and anodic, are generated by changing the direction of the current that flows through the tissue. An example of the H-bridge switches' configuration for one phase is depicted in Fig. 4.2b. In this scenario, electrodes 2 and 4 are chosen as anodes, while electrode 3 is chosen as a cathode. By closing the upper H-bridge switches of electrodes 2 and 4 and the lower H-bridge switch of electrode 3, current can flow from electrodes 2 and 4, through the tissue, to electrode 3. In the next phase, to reverse the current flow, only the lower H-bridge switches of electrodes 2 and 4, and the upper H-bridge switch of electrode 3 will be closed (not depicted here).

The purpose of a balanced biphasic pulse is to inject and remove the same amount of charge needed to stimulate the nerves so as not to cause excess charge buildup at the ETI that might harm the tissue and damage the electrode [22]. For this reason, it has been customary in the design of neural stimulators to balance the two stimulation phases as accurately as possible [33], while also including a coupling capacitor to prevent charge buildup [34]. However, even a perfectly balanced biphasic pulse will not always guarantee the absence of harmful electrochemical reactions, given the non-linear nature of the ETI. To mitigate this, stimulator designs started introducing features that aim at actively reducing any charge buildup that leads to a voltage offset detected by the electronic system at its output after the end of a stimulation pulse [35].

A good practice to minimise the charge buildup is by eliminating the offset at the electrodes connected to the output terminals of the system by means of negative

feedback [36]. Ideally, any electrode voltage offset should be minimised versus a non-polarisable reference electrode with a stable potential at the tissue side. Here, in the absence of in vivo non-polarisable reference electrodes, one of the electrodes of our system is defined as reference, placed at the tissue and gets assigned a stable potential, against which the potential at every stimulating electrode is compared. By bringing all other electrode potentials to the potential of the reference electrode, all inter-electrode voltages are close to zero, thus reaching a zero net charge at the stimulation site. To achieve this, a circuit is needed to monitor the voltage at each electrode.

A second-order active low-pass filter (LPF) in a Sallen–Key topology is placed behind each electrode to monitor the electrode’s voltage with respect to ground and to forward this voltage to the MCU for further processing. Each filter consists of one unity-gain OpAmp, part of the TLV9044 quad-channel OpAmps, and two RC networks. By choosing the RC network values at $R = 1\text{ M}\Omega$ and $C = 15\text{ nF}$, the cut-off frequency f_c of the LPF is set at approximately 10 Hz, since

$$f_c = \frac{1}{2\pi RC}. \quad (4.1)$$

Given the low f_c of the filter, as well as its order, which leads to an attenuation by 40 dB/decade, this essentially allows for a DC measurement of the electrode voltage.

As previously mentioned, to achieve a zero potential difference between the stimulating electrodes and, thus, a zero average differential output voltage at the stimulation site, the resting potential of all electrodes needs to be at the same level. For this, the measured electrode voltage is compared to a reference voltage V_{ref} . This V_{ref} is set halfway between the supply voltage and ground, as the common-mode output voltage, and assigned to the reference electrode. When powering with US, the supply voltage corresponds to the voltage V_{rect} that is generated by harvesting the acoustic energy, converting it to the electrical domain and rectifying the resulting sinusoidal signal. Consequently, V_{ref} is set at $V_{\text{rect}}/2$.

To ensure a reliable V_{ref} , an accurate reading of the supply voltage V_{rect} is needed. An active LPF with a cut-off frequency of $f_c = 10\text{ Hz}$ provides a precise value of V_{rect} . A voltage divider contributes to the LPF behaviour while producing the necessary $V_{\text{rect}}/2$ to be used as V_{ref} . Finally, this value is forwarded to the MCU, where the necessary actions are taken to obtain a zero net charge between all electrodes of the stimulation site.

Every electrode of the output stage is controlled by one side of the H-bridge, giving the possibility to set each electrode individually as anode or cathode. This feature makes spatially selective stimulation feasible, as the selection of more than one electrode as an anode can help manipulate the generated electric field and concentrate it to a specific region within the nerve, as seen in Fig. 4.2b.

The main specifications of the complete system are summarised in table 4.1.

4.2.2. GRAPHICAL USER INTERFACE

A GUI is used to define the stimulation settings, as seen in Fig. 4.2c. The visual part of the GUI is designed using the PySide6 Designer. Using the designer’s interface,

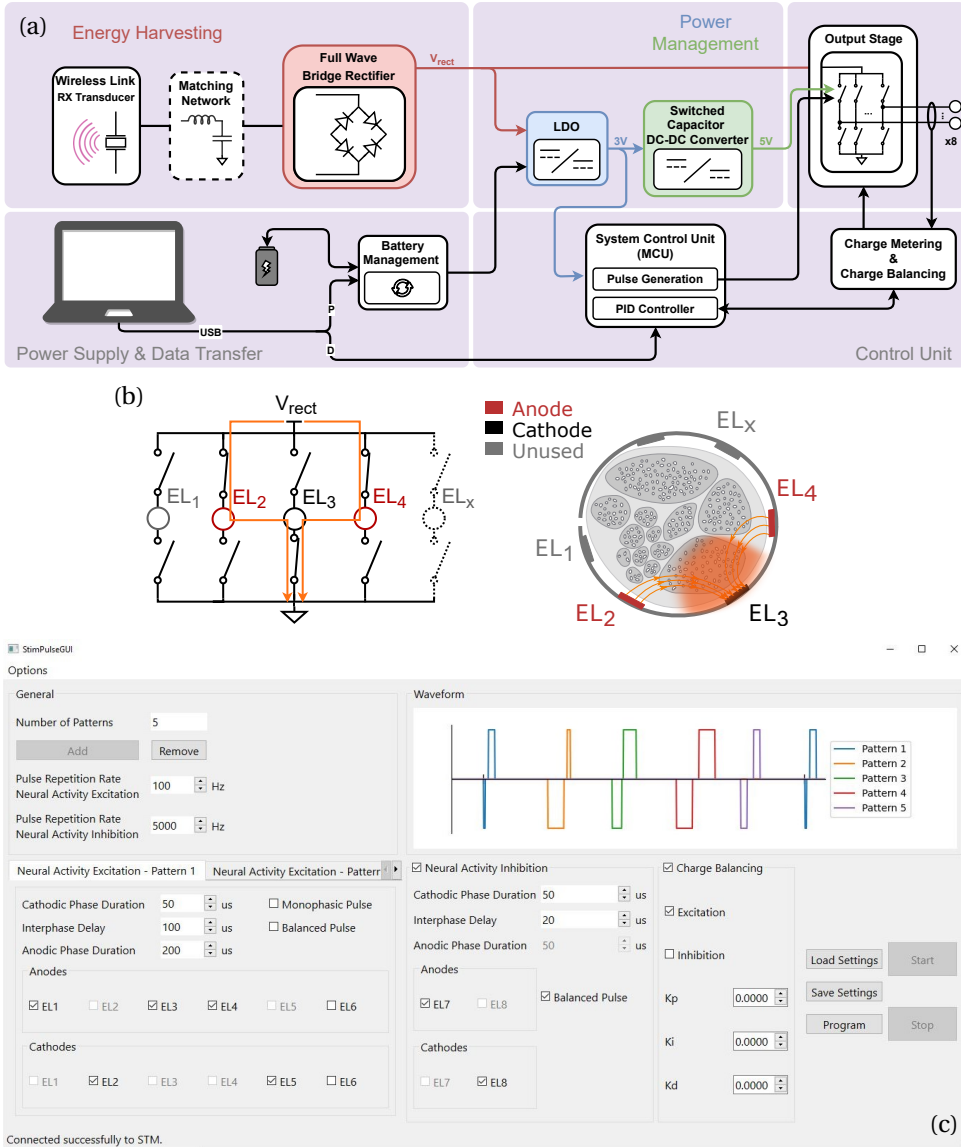


Figure 4.2: a) System-level block diagram of the proposed neuromodulation platform and its electrical functionalities. The platform can be powered wirelessly through ultrasound (US), using the same signal for powering and stimulation. For testing purposes and for the identification of all relevant stimulation parameters, the US signal can be emulated through a function generator, while the rest of the system can be powered through a battery or a USB connection. The user can communicate with the platform through a GUI on a laptop or PC through the same USB connection. b) The possibility to customise the configuration of the electrodes used for neural activity excitation allows for manipulation of the generated electric field, leading to spatial selectivity of the activated area. Here, electrodes 2 and 4 are chosen as anodes, while electrode 3 is the cathode, concentrating the electric field and stimulation area around electrode 3. c) Screenshot of the GUI used to configure the stimulation parameters.

Table 4.1: *Neuromodulation platform specifications overview.*

Parameter	Value
Nr. of electrodes A ^a	6
Nr. of electrodes I ^a	2
Pulse pattern	Mono-/biphasic symmetric/asymmetric
Pulse polarity	- (cathodic) or + (anodic) first
Pulse width	0 - 1500 μ s (in 1 μ s steps)
Interphase delay	5 - 200 μ s (in 1 μ s steps)
PRR ^b A ^a	1 Hz - 1 kHz
PRR ^b I ^a	1 kHz - 50 kHz
Supply	Wirelessly through US ^c LiPo ^d 3.7V 2 mAh cells (rechargeable) 5V through USB

^aA and I denote Activation and Inhibition, respectively.^bPulse Repetition Rate.^cUltrasound.^dLithium Polymer.

all necessary windows, text fields, and buttons are selected and arranged in the desired pattern. From this design, the “.ui” files are generated and subsequently imported into Python, where all windows, buttons, and fields are linked to their functions, allowing the GUI to operate as intended. The library of the Protocol Buffers (protobuf), a mechanism for serialising structured data, is used so that the GUI can communicate with the MCU.

Through the GUI, the parameters for the neural activity excitation and inhibition can be set. Each of the stimulating electrodes can be individually selected and defined as either anode or cathode. At least one of the electrodes needs to be selected as anode and one as cathode to ensure current flow between the electrodes. An electrode cannot have both anode and cathode status to avoid shorting at the stimulation site.

To increase flexibility in the stimulation pulse sequence, up to five different biphasic pulse patterns can be programmed within one time period, as seen on the waveform visualisation in Fig. 4.2c. These five stimulation patterns can be used only for the purpose of neural activity excitation, and their parameters can be configured for each pattern individually. Among those configurable parameters are the pulse repetition rate (PRR), i.e., the time frame in which all patterns are repeated, the cathodic and anodic phase duration and the interphase delay duration, and finally, the selection of the electrodes and their allocation as anodes or cathodes. The same parameters can be configured for inhibitory patterns, which can be activated and deactivated depending on the stimulation needs.

4.2.3. FIRMWARE

The STM32L562 microcontroller (μC) is programmed in C language using the STM32CubeIDE 1.9.0.

4.2.3.1. STIMULATION PULSE GENERATION

The timers of the μC are used to provide the control signals for stimulation. By using the complementary pulse width modulation (PWM) function of the timers, a biphasic signal can be generated using the regular channel output (TIMx_CHy) for the first phase and the complementary channel output (TIMx_CHyN) for the second phase of the biphasic pulse. A dead time (DT) can be inserted between the two outputs, acting as an interphase delay and ensuring that the two outputs are not active simultaneously. The advanced-control timers TIM1 and TIM8 are used for the excitatory and the general-purpose timer TIM15 for the inhibitory signals. Timers TIM1 and TIM8 each have three channels, all with a regular and a complementary output, while timer TIM15 has two channels, out of which only one has a complementary output.

To achieve the necessary flexibility for spatially selective stimulation, each μC channel controls only one side of the H-bridge, i.e., one electrode at the output stage. Here, the regular channel output TIMx_CHy controls the upper switch and the complementary channel output TIMx_CHyN controls the lower switch. Therefore, a total of six μC channels (TIM1 and TIM8) can control a maximum of six electrodes used for excitation.

Responsible for triggering, and thus the synchronised start, of the timers TIM1 and TIM8 is the general-purpose timer TIM4. Whenever TIM1 or TIM8 are triggered by TIM4, the first phase of the biphasic pulse commences (TIMx_CHy is “high”), together with the incrementation of each timer’s own counter. The first phase ends when reaching the value of the CCR register, at which point, the timer changes polarity (TIMx_CHyN is “high”). A dead time can be assigned as an interphase delay between the two phases of the pulse. The second phase commences right after the dead time, with its end being indicated by the interrupt service routine (ISR) of TIM1, which is called at the moment the timer counter overflows. The length of the second pulse is defined as

$$t_{\text{second,phase}} = t_{\text{period,TIM1}} - t_{\text{first,phase}} - t_{\text{DT}}. \quad (4.2)$$

In a similar manner, the general-purpose timer TIM3 triggers the start of the biphasic pulse for the inhibition, conducted by TIM15. The ISR of TIM15 ends the pulse. As there are only two electrodes for inhibition, their control can be achieved by a single H-bridge. Thus, the architecture that is used for excitation, enabling the combination of different electrodes, is no longer needed. Instead, a single μC channel, connected to both electrodes, is sufficient to perform the switching. For this, one of the two μC channels of TIM15 is needed, the one with the complementary output.

Whenever the electrodes for inhibition are not stimulating, they are left floating to prevent any current flow between them, which is achieved by leaving all channels open. When the electrodes for excitation are not stimulating, they are grounded to remove any remaining charge built up. This is achieved by connecting all complementary channels TIMx_CHyN, and thus the lower part of the H-bridge, to ground. The latter approach cannot be implemented for the inhibitory electrodes, as the switches of the H-bridge used for inhibition cannot be individually controlled. The timings and dependencies of the timers and the resulting H-bridge control are illustrated in Fig. 4.3a.

4.2.3.2. PID CONTROLLER FOR CHARGE BALANCING

4

A charge balancing scheme is implemented to remove as much excess charge as possible from the ETI after a stimulation cycle, which might cause irreversible reactions to either the tissue or the electrode. The particularity of this design is that the signal used for neural stimulation is directly derived from the signal used for powering the device and, therefore, its amplitude depends on the intensity of the harvested US signal and cannot be changed during stimulation. As a result, in order to modify the amount of charge injected into the tissue, only the duration of the pulses can be adapted accordingly.

This pulse width adaptation is conducted by a digital PID controller running on the μC , which regulates the pulse width of both phases of every upcoming biphasic pulse to avoid excess charge buildup. Generally, a control loop is used to bring a specified physical variable, the measured process variable (PV), to a desired value (set-point (SP)) and maintain it at that, regardless of disturbances. In order to fulfil the control task, the instantaneous value of the PV must be measured and compared with the SP value. Any deviations from the desired SP are re-adjusted accordingly through the controller's output.

Here, the desired SP is $V_{\text{rect}}/2$, as explained in section 4.2.1. The PV is the voltage measured at each electrode of the output stage. This voltage is sampled during stimulation, acting as feedback to be compared with the desired SP. Before any of the signals can be processed by the μC , the measured PV and SP must first be digitised using an analog-to-digital converter (ADC). With the ADC clock frequency at 20 MHz and the sampling time set at 640.5 clock cycles (total conversion time = sampling time + 12.5 ADC clock cycles), the ADC can sample every $32.65\mu\text{s}$. The necessary ADC conversions amount to 9, one for the voltage of each of the PVs plus one for the SP, $V_{\text{rect}}/2$. Given this number and the ADC sampling time, the ADC needs a total of $293.85\mu\text{s}$ for all 9 conversions, which corresponds to a sampling rate of approximately 3.4 kHz. Choosing this relatively low sampling rate for the ADC is beneficial in terms of energy efficiency. Given that the measured PV can be considered a DC measurement (because it is LP-filtered at 10 Hz), minimising the effective sampling rate of the ADC to 3.4 kHz reduces the overall power consumption.

Finally, the output signal is calculated by the digital controller. This output dictates the amount of time by which the cathodic and anodic phases need to be increased or decreased to mitigate any leftover potential difference between the electrodes.

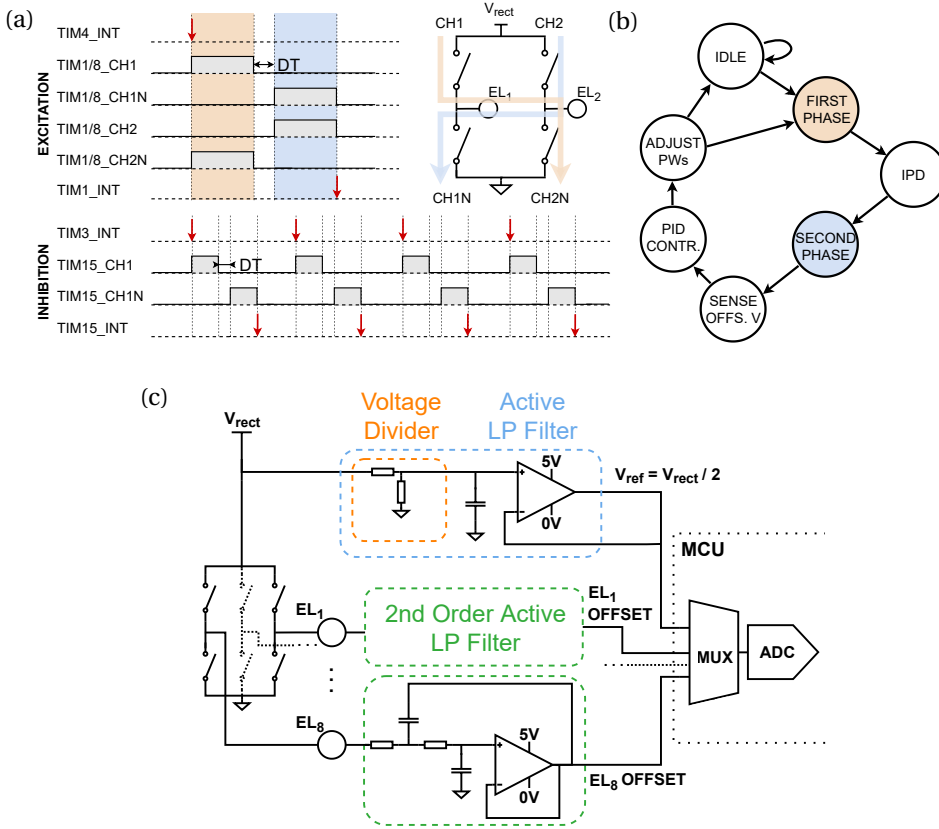


Figure 4.3: a) Time diagram of the biphasic stimulation pulse generation within the STM32L562 μ C. The ISR of the general-purpose timer TIM4 triggers the start of the advanced-control timers TIM1 and TIM8 that control the excitatory electrodes. The first stimulation phase (orange) is followed by the interphase delay, set by the dead time register of the microcontroller, and by the second phase (blue), thus controlling the two sides of the H-bridge at the output stage. The biphasic pulse ends with the ISR of TIM1, which is called at the overflow of the timer counter. The same routine is followed for the timers that control the inhibitory electrodes. b) FSM representation of a biphasic pulse sequence and the control loop actions for charge balancing. c) Detail of the output stage and the circuitry used to accurately measure the values needed for charge balancing. The electrode voltage at each electrode is measured with a second-order active low-pass filter and is compared to a reference voltage V_{ref} for the purpose of achieving a zero potential difference between any stimulating electrode pairs. V_{ref} is equal to $V_{rect}/2$, obtained by passing V_{rect} through a voltage divider and an active low-pass filter.

Since the total pulse width of one biphasic pulse (cathodic phase + interphase delay + anodic phase) is fixed due to the chosen method of generating these pulses (see equation 4.2), for charge balancing, only the ratio between the phases of each pulse can be adapted. The controller measures the PV after every stimulation pulse, compares it to the SP and computes the pulse width adaptation for the next pulse.

The finite state machine (FSM) in Fig. 4.3b illustrates the process of the biphasic pulse generation and the charge balancing method using the PID control loop. Starting from the IDLE state, the first phase of the biphasic pulse commences as soon as the command is sent through the GUI. Based on the chosen electrode configuration, this can be defined as either anodic or cathodic. The first phase is followed by the interphase delay and the second phase of opposite polarity. The value of the sampled electrode voltage is sent as feedback to the PID controller, which outputs the amount of time by which the two phase durations need to be adjusted. If the stimulation sequence is stopped, the system returns to the IDLE state; otherwise, it continues with the generation of the next biphasic pulse.

The digital implementation of the PID controller in the μC requires the standard form of the PID controller to be implemented in a discrete-time fashion. The equation for the discrete-time system is created based on the equation for the continuous system. Through the approximation of the individual terms by using backward finite differences, the discrete implementation of the controller output equation results in

$$u[n] = \underbrace{K_P \cdot e[n]}_{\text{proportional t.}} + \underbrace{K_I \cdot T_S \cdot \sum_{k=0}^n e(k)}_{\text{integral t.}} + \underbrace{\frac{K_D}{T_S} \cdot (e[n] - e[n-1])}_{\text{derivative t.}}, \quad (4.3)$$

comprised of the proportional, integral and derivative terms, where K_P , K_I and K_D denote the proportional, integral and derivative gain, respectively. e indicates the error signal that the controller uses to calculate its output, which is the difference between the measured PV and the desired SP. T_S is the sampling time between two sampling points and n indicates the sampling number. The controller output value is then added to or subtracted from the pulse width of the cathodic or anodic phase. The controller is furthermore equipped with an anti-windup mechanism; when the integral term reaches saturation, either at its upper or lower bound, it is clamped to the corresponding predefined limit. As a result, the integral term cannot grow uncontrollably.

The mechanism for charge balancing can be activated or deactivated through the GUI. Furthermore, the GUI allows for the modification of the proportional, integral and derivative gains, adjusting them accordingly to fit the individual needs of the electrodes interfacing with the neuromodulation platform and the stimulation pattern characteristics. Finally, any of the K_P , K_I or K_D gains can be set to zero, allowing for a different version of the controller.

4.2.4. SYSTEM VALIDATION

To validate the functionality and performance of the neuromodulation platform, experiments are conducted in two different configurations. For the first one, the US signal is emulated either in its harvested AC form through a function generator (33622A, Keysight) or in its rectified form through a power supply - either a laboratory power supply (EDU36311A, Keysight) or the available USB connection. This gives a clear overview of the functionality of the individual components of the platform.

For the second configuration, the platform is entirely powered through US. Two commercially available transducers by Precision Acoustics, suitable for immersion use, are used as the transmitter (TX) and receiver (RX). The TX has a diameter of 19 mm and a resonance frequency of 2 MHz, matching the resonance frequency of the RX that has a diameter of 15 mm. Both the TX and the RX are immersed in a tank filled with deionised (DI) water. The water tank is layered with acoustic absorbers (VK-76000, Gampt), to eliminate the unwanted reflections that could influence the results of the measurements.

The output of the neuromodulation platform, as well as all intermediate signals, are displayed on an oscilloscope (MDO34, Tektronix and RTA4004, Rohde&Schwarz). The parameters for a stimulation protocol are set and changed through the GUI on a laptop. Fig. 4.4 illustrates the setup used for all measurements.

For the initial system validation measurements, the load connected to the output stage is purely resistive. All further measurements are conducted with electrodes submerged in a phosphate-buffered saline (PBS) solution (0.14 M NaCl, 2.7 mM KCl, 10 mM phosphate buffer, with a pH value of 7.4 ± 0.05), which mimics the physiological environment of the inner body. The electrodes used are the dorsal root ganglion (DRG) leads from Abbott® (Proclaim™ DRG), equipped with 4 electrodes. All 4 electrodes are characterised prior to the validation measurements through electrochemical impedance spectroscopy (EIS), with the graph in Fig. 4.5 presenting an EIS measurement between 2 adjacent out of the 4 electrodes.

4.3. RESULTS

4.3.1. WIRELESS LINK CHARACTERIZATION

To successfully power the neuromodulation platform with US, the performance of the wireless US link is assessed. Fig. 4.6a illustrates the TX and RX voltage, $V_{TX,pp}$ and $V_{RX,pp}$, respectively, along with the rectified voltage V_{rect} that is eventually used to power the platform. This measurement is conducted in an open-circuit configuration, reducing the voltage losses to a minimum and providing an indication of the maximum available power that can be transferred in this configuration. Here, for a $V_{RX,pp} = 10.65V$, we obtain a $V_{rect} = 9.72V$ - given that the diodes of the bridge rectifier and the parasitic capacitances of the RX transducer form a voltage multiplier.

Furthermore, the obtained rectified voltage V_{rect} is observed as a function of the voltage at the US RX $V_{RX,pp}$ when connecting it to different loads. V_{rect} is measured

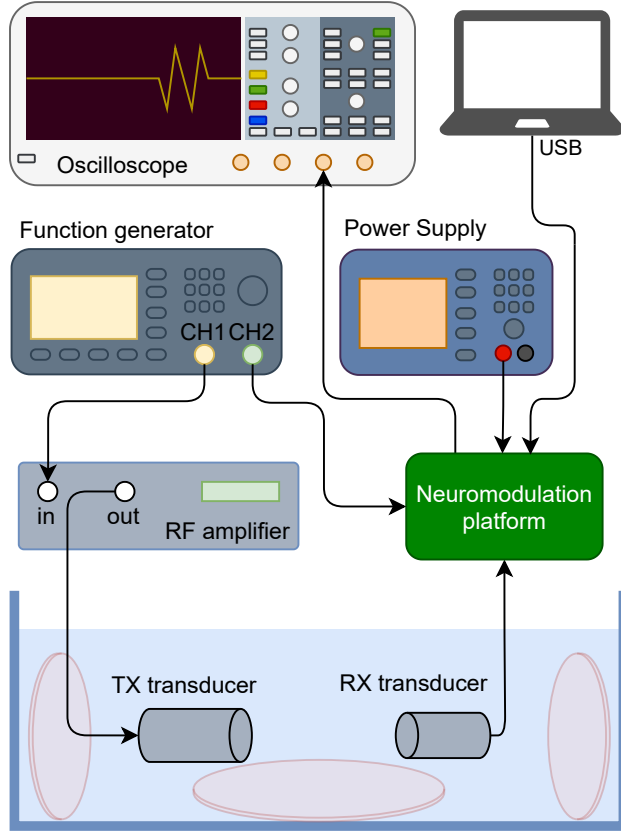


Figure 4.4: Schematic of the measurement setup for the functionality validation of the neuromodulation platform.

in an open-circuit configuration, for three different resistive loads, and finally for when the rest of the platform is connected and acts as a load. For the last case, $V_{RX,pp}$ is increased only until V_{rect} reaches the value of 5.5V, which is the maximum voltage that can serve as an input to the LDO that follows the rectifier on the platform. Fig. 4.6b depicts the development of V_{rect} with an increasing $V_{RX,pp}$.

4.3.2. PID CONTROLLER BEHAVIOUR AND CHARGE BALANCING

The PID controller used for charge balancing is parametrised empirically using the DRG leads from Abbott[®] submerged in a PBS solution. One of the electrodes on the Abbott[®] DRG leads is connected to the reference voltage V_{ref} (here at $V_{rect}/2$) that is used as the SP. That way, we provide a stable potential within the same environment as the stimulating electrodes, against which we can compare the measured electrode voltage to eliminate any potential difference between all electrodes. The behaviour

of the controller is analysed for different proportional, integral and derivative gains, resulting in an optimum combination for the particular application.

Starting with the tuning of the proportional gain K_P , K_P is adjusted while K_I and K_D are set to zero. K_P is gradually increased, resulting in an increasingly aggressive controller. With the response of the control loop becoming more reactive, the deviation of the PV from the desired SP becomes smaller until the system becomes unstable and starts to oscillate. Fig. 4.7a demonstrates this behaviour for seven different K_P values. $K_P = 0.8$ is chosen to continue the tuning for the integral and derivative gains, as it approaches the desired SP the closest and without oscillations.

With K_P set as 0.8, K_I is now varied while K_D remains zero. Similarly to the settings for K_P , as the value for K_I increases, so does the aggressiveness of the controller. A too-low value leads to a (possibly too) slow settling of the controller, while a too-high value leads to large oscillations and unstable behaviour, as can be seen in Fig. 4.7b. Furthermore, a higher than necessary K_I value can lead to a large overshoot and potentially the injection of a higher voltage that might harm the stimulated tissue. K_I was chosen as 0.004, for which the controller settles quickly to the desired SP without any oscillations or overshoot.

Finally, the same procedure is followed for the derivative gain K_D . K_D is varied over six values, with no significant changes for lower K_D values, as can be seen in Fig. 4.7c. When increasing the value for K_D , the controller starts becoming unstable. For this reason, K_D is set to 0.001. All gains can be varied as needed, depending on the application and type of electrodes that the tuning is intended for.

After tuning the controller to the intended measurement setup, the potential difference between all stimulating electrodes is measured for a variety of settings. The maximum potential difference is calculated and compared between having the charge balancing mechanism deactivated and activated. For this, we varied the PRRs

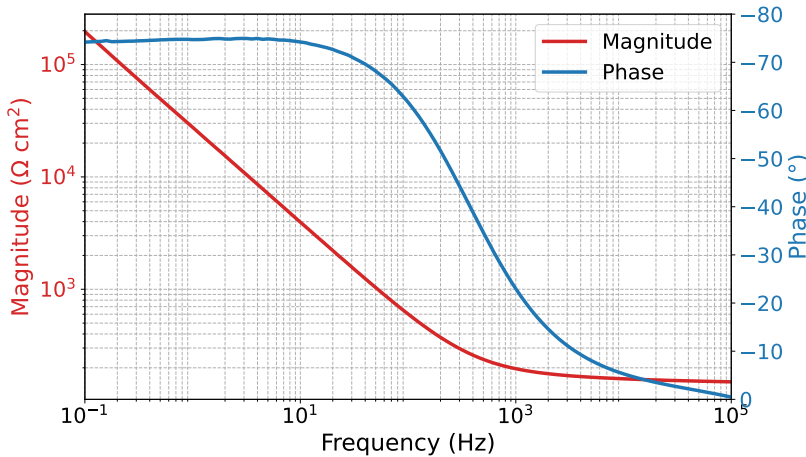


Figure 4.5: *electrochemical impedance spectroscopy (EIS) of the DRG leads from Abbott® (Proclaim™ DRG).*

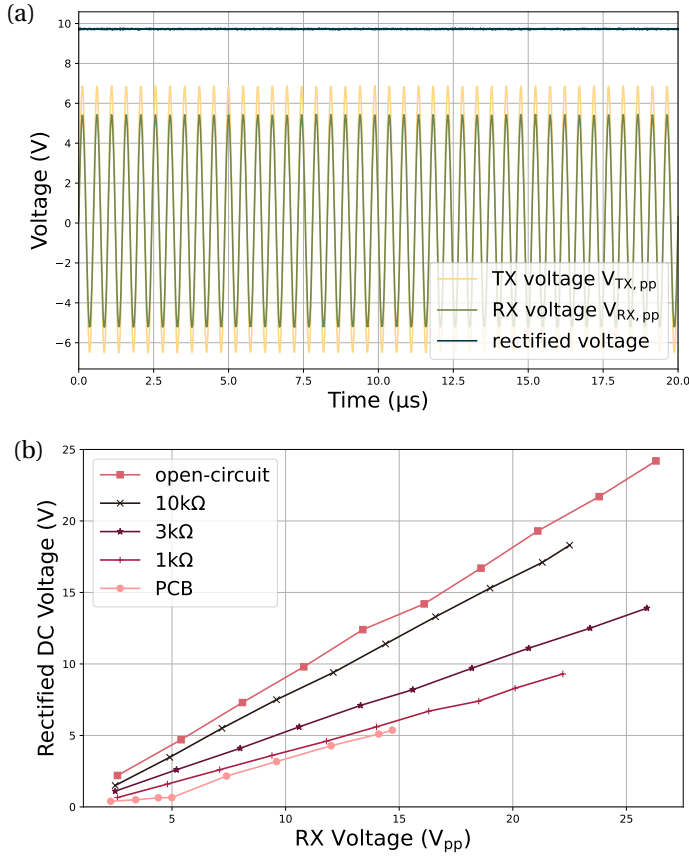


Figure 4.6: a) Representation of the voltage at the US transmitter TX $V_{TX,pp}$, the voltage at the US receiver RX $V_{RX,pp}$ and the rectified voltage V_{rect} that is used to power the neuromodulation platform, with the measurement conducted in an open-circuit configuration. b) Development of the rectified voltage V_{rect} as a function of the voltage at the US receiver RX $V_{RX,pp}$ when connecting to different loads.

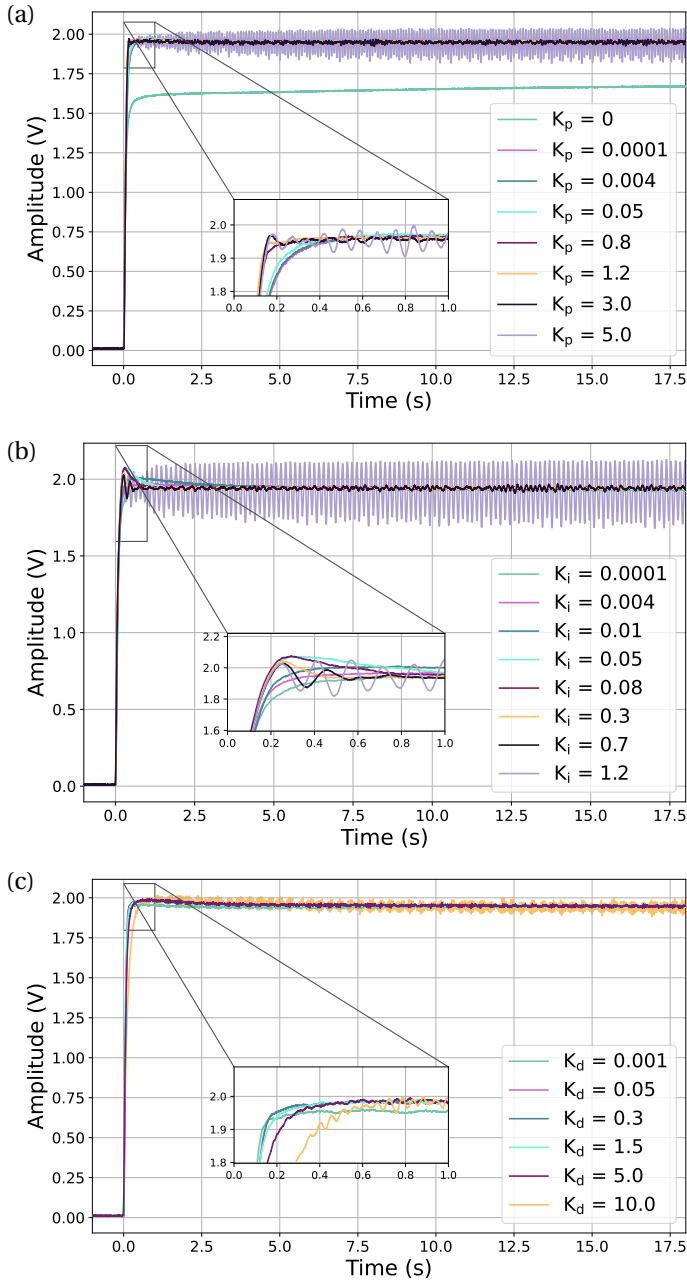


Figure 4.7: Parametrisation of the PID controller used for charge balancing. a) K_p is varied over multiple values. For $K_p = 0.8$, the deviation between the PV and the desired SP decreases without the controller oscillating. b) K_i is varied over multiple values. For $K_i = 0.004$, the controller settles faster without unwanted oscillations or instability. c) K_d is varied over multiple values. For $K_d = 0.001$ the controller settles slightly faster to the desired SP.

(100Hz vs. 1kHz) of the stimulation pulses, as well as the number of patterns employed for every stimulation sequence (1, 3 and 5 patterns (1P/3P/5P) for a PRR of 100 Hz, and 1 and 2 patterns (1P/2P) for a PRR of 1 kHz). Fig. 4.8 demonstrates the effectiveness of the employed charge balancing mechanism, lowering the potential difference for lower PRRs (100 Hz) from approximately 300 mV to 3 mV, and for the higher PRRs (1 kHz) from approximately 200 mV to 2 mV, where all values are mean values.

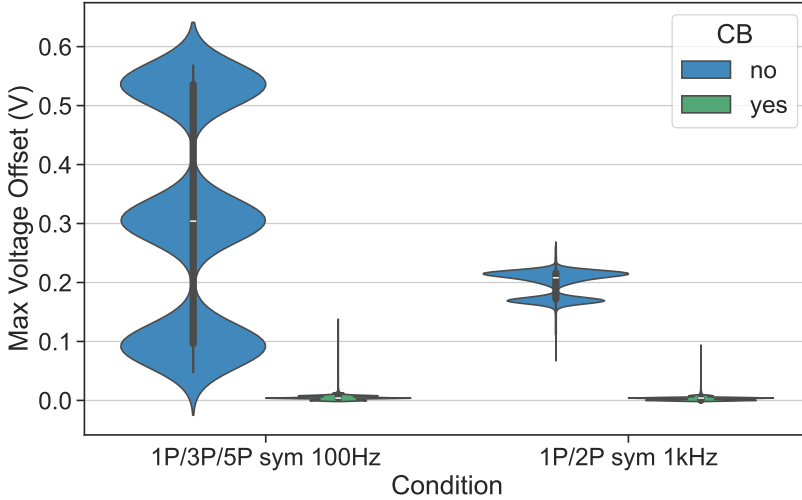


Figure 4.8: Maximum potential difference (voltage buildup due to charge accumulation) between stimulating electrodes without and with the charge balancing mechanism activated.

4.3.3. SYSTEM OUTPUT PERFORMANCE

4.3.3.1. BIPHASIC PULSE AND MULTICHANNEL OPERATION

The output of the neuromodulation platform, as well as all intermediate signals, are displayed on an oscilloscope (MDO34, Tektronix and RTA4004, Rohde&Schwarz). The parameters for a stimulation protocol are set and changed through the GUI on a laptop. Fig. 4.4 illustrates the setup used for all measurements. Up to a total of five different patterns can be activated for neural excitation within one stimulation period, allowing for interleaved stimulation. Each pattern can have an independent set of parameters, thus addressing a different group of electrodes while having a different pulse width and interphase delay. An illustration of the patterns appears on the GUI, as shown in Fig. 4.2c, to aid the user in visualising the programmed stimulation protocol. Furthermore, the output stage of the platform can connect to two electrodes for neural activity inhibition, and the connection can be activated or deactivated at will. The biphasic pulse generation and the flexibility of the multichannel operation are evaluated while powering the platform through the USB

connection and emulating the US signal used for stimulation through the 33622A Keysight function generator (signal amplitude of 2 V).

Fig. 4.9 shows the measured voltage at the platform's output when all 5 patterns are being engaged, with the settings corresponding to the ones displayed in Fig. 4.2c. This graph demonstrates the accuracy of the neuromodulation platform in producing the desired patterns and the possibility of engaging up to 5 stimulation patterns within one period of a stimulation protocol. The plot shows the measured voltage when connecting the platform's output to purely resistive loads of 1 k Ω and 100 k Ω . Even though multiple electrodes can be engaged within one pattern, Fig. 4.9 only demonstrates the voltage measured between two electrodes, for ease of comparison with Fig. 4.2c.

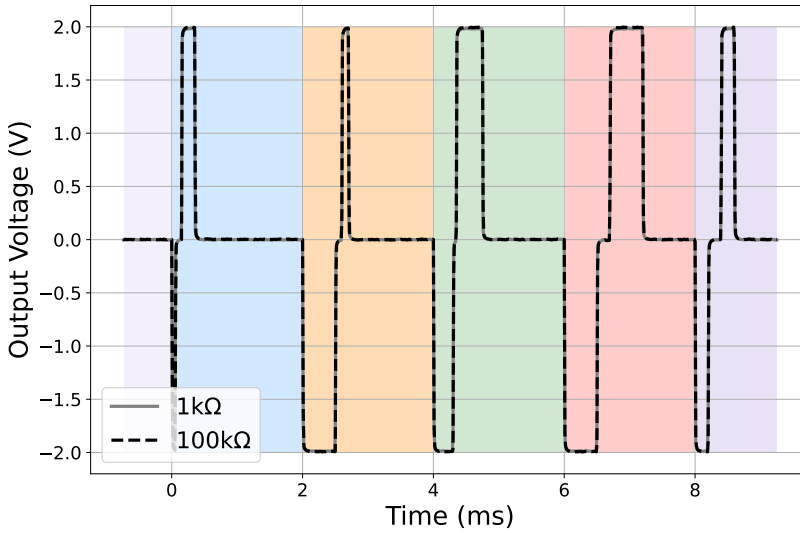


Figure 4.9: Measured voltage output of the neuromodulation platform, intended for neural activity excitation, when connected to a resistive load. Here, all five available patterns are activated, with the shaded areas corresponding to the colours of the respective pattern as displayed on the GUI.

4.3.3.2. ELECTRODE VOLTAGE OUTPUT

To evaluate the performance of the neuromodulation platform, the system is powered wirelessly through US, with the signal used for powering being forwarded to the output stage for stimulation. The output stage of the platform is connected to the DRG leads from Abbott[®], submerged in a PBS solution to emulate the environment of the inner body. Part of the setup used for the system's characterisation is depicted in Fig. 4.10.

Given that the voltage V_{rect} used for powering the platform is also used for stimulation, the stimulation pulses have an amplitude that is dependent on the

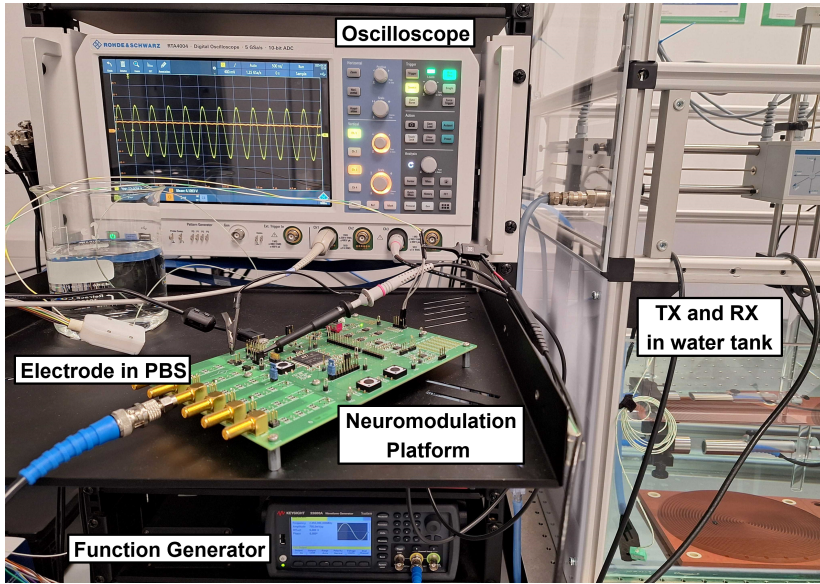


Figure 4.10: Neuromodulation platform characterisation setup. The function generator drives the US transmitter TX, and the US receiver RX is connected to the platform for powering. Both the TX and RX are immersed in a water tank. The output of the platform is connected to the DRG leads from Abbott®, which are submerged in a PBS solution. The oscilloscope aids in visualising the system's output.

intensity of the harvested US signal. In the event of transducer misalignment or movement, the harvested power might fluctuate, affecting the stimulation pulse amplitude. To ensure that the necessary amount of charge needed for neural stimulation is delivered within one stimulation pulse, the pulse width is scaled according to the varying V_{rect} . Consequently, the pulse width of each stimulation phase will become longer for a lower V_{rect} , or shorter for a higher V_{rect} . Fig. 4.11a demonstrates the implemented scaling at the example of four different voltages V_{rect} .

Finally, the system's output is observed when stimulating with the charge balancing mechanism deactivated and activated. At the example of one pulse within a stimulation sequence with a PRR of 100 Hz, the voltage offset between stimulation pulses decreases considerably while reducing the pulse width of the second (here, anodic) phase of the biphasic pulse. Fig. 4.11b shows the measured output between two electrodes, without and with the charge balancing activated.

4.4. DISCUSSION

The presented platform offers a readily reproducible and versatile neuromodulation system that can be used to further explore the possibilities that VNS has to offer. Using only commercially available components, we developed a system that is

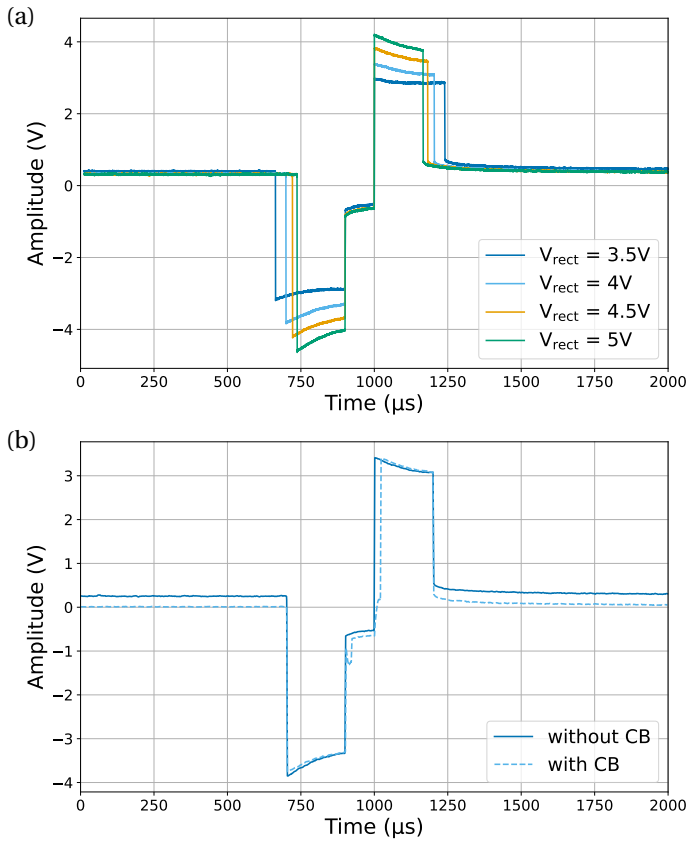


Figure 4.11: *a) Measured voltage output of the neuromodulation platform for a varying V_{rect} - the voltage used both for powering the platform and stimulating the electrodes connected to the output stage. The pulse width of each phase (cathodic and anodic) decreases/increases with increasing/decreasing V_{rect} , respectively. b) Difference in the measured voltage output of the neuromodulation platform when having the charge balancing mechanism deactivated and subsequently activated. Here, we observe one biphasic pulse as part of a pulse sequence with a pulse repetition rate (PRR) of 100 Hz, and it is visible that the voltage offset between biphasic pulses is reduced significantly when activating the charge balancing (CB) mechanism.*

intended for simultaneously exciting and inhibiting neural activity, while offering the possibility to connect it to multiple stimulating electrodes.

Powering the platform wirelessly through US opens the way for a future miniaturisation and exploration of US-powered neuroelectronic implants that include only the most essential and power-efficient components needed for the intended application. Here, the wireless power transfer link consists of a commercially available US transmitter and US receiver, with an electrical impedance of 50Ω . Though the platform allows for the incorporation of a matching network, this was not needed in this configuration. Working towards a miniaturised implant, the bulky

commercial US receiver can be replaced by integrated piezoelectric or capacitive micromachined ultrasound transducers (PMUTs or CMUTs, respectively) [37, 38], which will require the introduction of a matching network. In this case, it will be important to consider the broader implications of the powering scheme. One potential concern is tissue heating due to ultrasound absorption, underscoring the importance of maintaining exposure levels well below the FDA's limits for ultrasound. Additionally, an investigation of the power efficiency of the US link will be required, which will depend on factors such as the specific transducer design and alignment [37, 39].

The choice to use the same signal for powering and stimulation can improve the power efficiency of the system, especially in a future, miniaturised scenario, where the power consumption is dominated by the neural stimulation. Unlike conventional constant-current or constant-voltage stimulators, the proposed design does not require additional power regulation, thus eliminating conversion losses. The voltage harvested through US powering is applied directly for stimulation, and the charge delivery can be adjusted via pulse width modulation without increasing the instantaneous power demands. Thus, any losses are limited primarily to the MCU operation, which defines the stimulation sequence. Still, this comes at the cost of a stimulation pulse amplitude dependent on the US signal intensity. This dependency removes one degree of freedom for defining the stimulation parameters. It can, however, be compensated for by adjusting the width of the stimulation pulses with respect to the available power, to ensure that the necessary amount of charge needed for stimulation is delivered to the tissue. The corresponding scaling in this implementation is linear; it can, however, also follow a different trend, e.g., that of the strength-duration curve [40].

Furthermore, the intensity of the received US signal is currently controlled through the definition of the sent US signal, ensuring that the resulting voltage is within the limits that the components of the platform can tolerate. The addition of a Zener diode in reverse bias can help to maintain this voltage within the required limits. By appropriately selecting the diode's breakdown voltage and maintaining the voltage output within a predefined limit, we furthermore avoid violating the electrochemical water window at the ETI. The Zener diode should serve only as a safeguard, with the on-board MCU monitoring the voltage and issuing a warning before the Zener threshold is reached. This ensures that the diode acts as a last-resort protection mechanism rather than a primary means of regulation.

The integrated charge balancing technique increases stimulation safety by pursuing a zero net potential difference between all stimulating electrodes. For this, we define a reference against which we compare the potential of every electrode and place all electrodes (stimulating and reference) within the same environment. By attempting to bring every electrode to the potential of the reference electrode, the voltage offset between the electrodes is significantly reduced when enabling charge balancing, achieving offsets as low as 2 mV. Still, this is only a safety measure and does not provide a safety guarantee, as with most charge balancing mechanisms.

Notable is the accumulated voltage offset difference between pulses with lower versus higher PRRs, when the charge balancing mechanism is not yet activated. As

can be seen in Fig. 4.8, the potential difference between the stimulating electrodes is higher for lower PRRs; here at 300 mV for 100 Hz versus 200 mV for 1 kHz. This value, however, does not correspond to the typically measured voltage offset in between stimulation pulses of a pulse sequence, but rather to the mean voltage offset value over a longer period. This is because, to estimate the DC component that might lead to harmful electrochemical reactions at the ETI and eliminate it, we use the mean value of the full signal, including the stimulation pulses, as approximated by the incorporated LPF. Therefore, even though a momentarily sampled voltage offset in between stimulation pulses would, as expected, measure lower for lower PRRs, the mean value over the full signal measures higher, given that this offset is present over a longer period when compared to a stimulation sequence with a higher PRR. By averaging the full signal, we take into consideration every instance of the stimulation pulse, including any hardware limitations (inconsistencies in the pulse widths, unwanted leakage currents, etc.) and the stimulation pulses themselves. The effectiveness of the chosen charge balancing mechanism is illustrated in 4.8, lowering the voltage offset, independent of the PRR or the number of stimulation patterns, to a few mV.

Currently, the developed neuromodulation platform can be used as a benchtop or in an intraoperative setting, as it still requires a connection to a laptop or PC to set the stimulation parameters through the GUI. A future design will include wireless communication to decouple the device from any external connections completely, as it can already be powered through a battery or wirelessly through US [41].

4.5. CONCLUSION

The neuromodulation platform presented in this work integrates wireless powering through ultrasound, spatially selective multi-electrode stimulation, and active charge balancing into a unified and reproducible benchtop system. Built entirely from off-the-shelf components and centered around a microcontroller, the platform uses ultrasound for energy transfer, with the same transferred and rectified signal also used for stimulation to enhance efficiency. It supports both excitation and inhibition of neural activity, employing multiple electrodes for spatially distributed stimulation, while the integrated charge balancing mechanism makes it suitable for extended experimental use. Beyond demonstrating each individual functionality, this work provides a practical and versatile experimental tool for investigating the functional potential of neuromodulation applications, including *vagus nerve stimulation* (VNS). Moreover, by combining these essential elements within a single system, it provides a solid basis for the future miniaturisation and translation to fully implantable, ultrasound-powered neuromodulation devices. While some of the design choices are specific to the current neuromodulation platform prototype, the core concepts introduced in this work, i.e., harvesting US for both energy transfer and stimulation, as well as the stimulation pattern generation and the charge balancing mechanism functionalities of the MCU, are intended to translate directly to future miniaturised implementations.

4.6. SUPPLEMENTARY NOTES

4.6.1. IN VIVO VALIDATION

The functionality of the platform is eventually validated in vivo on common earthworms (*Lumbricus* spp.). The earthworms are anaesthetized using a 10% ethanol solution and placed on a polyethylene foam base. The stimulating electrodes are placed at the anterior end of the worm, and the recording electrodes at the posterior end, separated by an electrode connected to GND, to reduce any stimulation artifacts [42]. The extended measurement setup used in these experiments is presented in Fig. 4.12, thereby enhancing the previously used setup shown in Fig. 4.4. The capability to stimulate the worm's nerve fibers is first evaluated using a commercially available constant current stimulator (DS8R, Digitimer). Upon the successful recording of the electrically evoked compound action potentials (eCAPs), the worm is stimulated using the neuromodulation platform. The eCAPs are recorded using a differential AC Amplifier (1700, A-M Systems) and a data acquisition interface (Power1401-3A, CED - Cambridge Electronic Design).

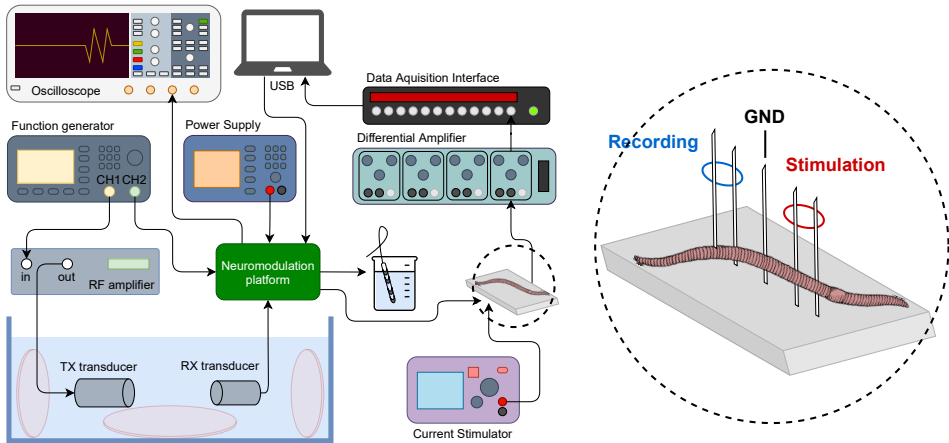


Figure 4.12: Extended schematic of the measurement setup for the functionality validation of the neuromodulation platform. The platform can be powered either using a lab power supply or through ultrasound using commercial transducers immersed in a water tank. To demonstrate its functionality, measurements are conducted with commercial electrodes submerged in a phosphate-buffered saline (PBS) solution, as well as in vivo on common earthworms. The stimulation parameters are set through the graphical user interface (GUI) on a laptop. The same laptop can be used to observe the stimulation response of the earthworms, as recorded by a differential amplifier.

Initially, a constant-current stimulator is used to elicit eCAPs in earthworm giant nerve fibers to establish a baseline response for comparison to the eCAPs produced when using the developed platform. The subsequent stimulation of the worms with the ultrasonically powered neuromodulation platform yields robust and

reproducible eCAPs, with the recorded signals closely matching those obtained with the commercial stimulator in both shape and amplitude. The stimulation was performed at a PRR of 1 Hz and for 5 subsequent pulses, using a pulse width of $200\mu\text{s}$ for each stimulation phase and an interphase delay of $50\mu\text{s}$. The amplitude of the stimulation pulse is defined by the harvested and rectified US signal V_{rect} , here measured at 4 V. Fig. 4.13 demonstrates the identified eCAPs sequence, as elicited by the neuromodulation platform. The inset of the figure shows the mean value and the standard deviation of the recorded eCAPs. Visible is the stimulation artifact at the beginning of the recorded signal, resulting in the median giant fiber response, followed by the lateral giant fiber response [43].

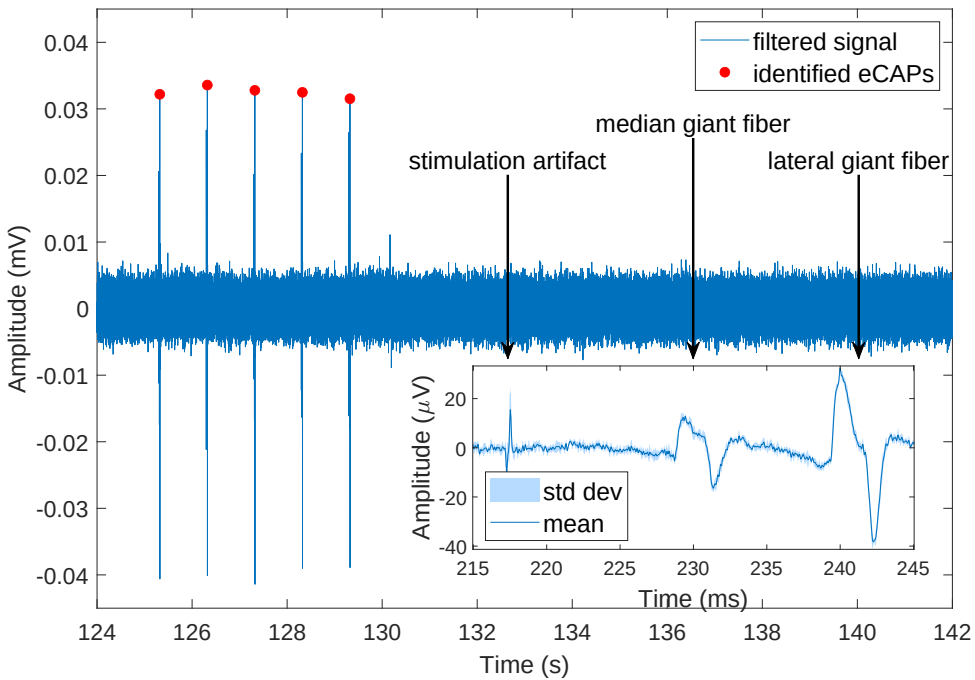


Figure 4.13: Successfully recorded and identified electrically evoked compound action potentials (eCAPs), induced when stimulating with the presented neuromodulation platform. A stimulation artifact is observed at the beginning of the recorded trace, followed by the response of the median giant fiber and the larger-amplitude lateral giant fiber response.

The in vivo validation experiments performed on common earthworms confirm the capability of the neuromodulation platform to evoke neural responses comparable to those elicited when using a commercially available electrical stimulator. This demonstrates the platform's capability of delivering sufficient charge to reliably activate peripheral neural pathways in vivo, verifying its ability to serve as a fully functional and effective wirelessly powered alternative for neural activation.

4.6.2. INFLUENCE OF THE OSCILLOSCOPE'S IMPEDANCE IN THE TRANSIENT VOLTAGE MEASUREMENTS

The input impedance of the oscilloscope can, in principle, influence the observed ETI potential, and thus the observed voltage offset, by introducing a leakage path to ground. To verify whether this effect is significant in this case, the conducted measurements are verified using a high-impedance probe that was constructed for this purpose.

The high-input impedance active probe uses the JFET input OPA828 operational amplifier (OpAmp) configured as a unity-gain buffer (or voltage follower). In this topology, the non-inverting input of the OpAmp is connected to the actual signal input, and the inverting input to the output of the OpAmp. The negative feedback ensures that the output voltage follows the input voltage with a closed-loop gain of 1 V/V. This topology provides a key advantage for measuring a node with an oscilloscope, namely its exceptionally high-input impedance. In this configuration, the OPA828 provides an input impedance of 1 T Ω , effectively isolating the measured node from the measuring system and minimising the influence of the oscilloscope probe on the signal. The simplified circuit diagram in Fig. 4.14 illustrates how the active probe interfaces with the output of the neuromodulation platform.

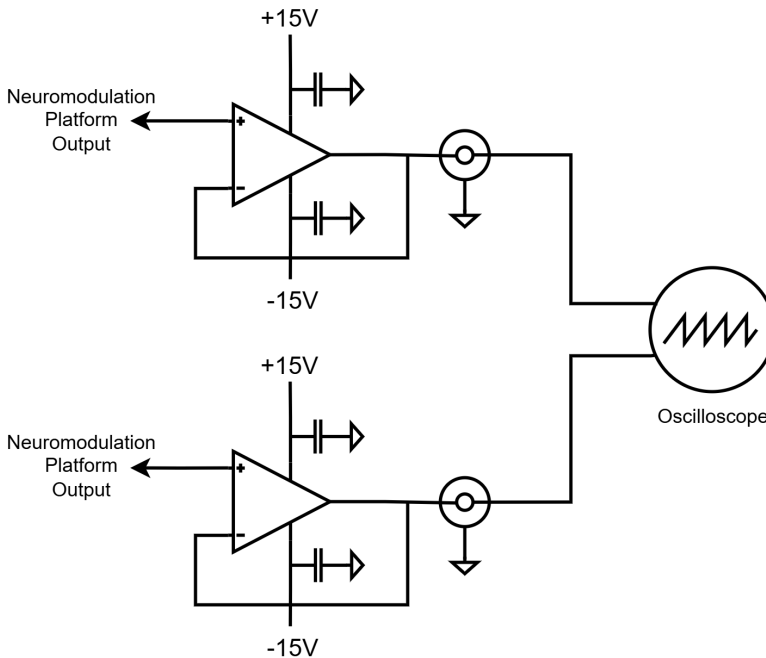


Figure 4.14: High-input impedance active probe using the JFET input OPA828 operational amplifier (OpAmp) configured as a unity-gain buffer, connecting the output of the neuromodulation platform to the oscilloscope.

To quantify the influence of the probe on the measurement results, we measure the output of the platform, connected to the dorsal root ganglion (DRG) leads from Abbott[®] (Proclaim[™] DRG) submerged in PBS, for three different scenarios: using the high-input impedance active probe ($1\text{ T}\Omega$), using the high-input impedance active probe while placing a $1\text{ M}\Omega$ resistor between the two measured channels, to emulate the typical oscilloscope probe impedance and, finally, with a differential probe (input impedance of $1\text{ M}\Omega$).

The results between the three cases did not differ noticeably, indicating that any leakage current through the oscilloscope probe is negligible compared to the currents involved at the ETI. This verifies the operation of the neuromodulation platform, as all recorded waveforms are consistent across repeated trials.

4.6.3. BILL OF MATERIALS (BOM)

The board contains 59 through-hole and 217 SMD components, leading to a total of 276 components. The high component count enables configurability to a high degree, allowing users to implement customised interconnections and adapt the system to their specific experimental requirements. As a result, the neuromodulation platform can be readily reconfigured to meet application-specific needs while maintaining reliable operation.

Table 4.2: Bill of Materials (BoM) for the replication of the neuromodulation platform.

Reference	Value	Footprint	Quantity
1	Capacitor 15n 25V C0G/NP0	C_0603_1608Metric_Pad1.08x0.95mm_HandSolder	26
2	Capacitor 100n 50V X7R	C_0603_1608Metric_Pad1.08x0.95mm_HandSolder	19
3	Capacitor 1u 25V X7R	C_0603_1608Metric_Pad1.08x0.95mm_HandSolder	10
4	Capacitor 2u2 10V X7R	C_0603_1608Metric_Pad1.08x0.95mm_HandSolder	5
5	Capacitor 10u 25V X5R	C_0603_1608Metric_Pad1.08x0.95mm_HandSolder	4
6	Capacitor 4u7 25V X5R	C_0603_1608Metric_Pad1.08x0.95mm_HandSolder	3
7	Capacitor 0u22 25V X7R	C_0603_1608Metric_Pad1.08x0.95mm_HandSolder	2
8	Capacitor 4u7 25V X5R	C_0805_2012Metric_Pad1.18x1.45mm_HandSolder	1
9	Capacitor 10n 25V C0G/NP0	C_0603_1608Metric_Pad1.08x0.95mm_HandSolder	1
10	Capacitor 0u47 25V X7R	C_0603_1608Metric_Pad1.08x0.95mm_HandSolder	1
11	Resistor 0 ^a	R_1206_3216Metric	36
12	Resistor 1M	R_0603_1608Metric_Pad0.98x0.95mm_HandSolder	25
13	Resistor 0 ^b	R_0603_1608Metric_Pad0.98x0.95mm_HandSolder	18
14	Resistor 100	R_0603_1608Metric_Pad0.98x0.95mm_HandSolder	8
15	Resistor 150	R_0603_1608Metric_Pad0.98x0.95mm_HandSolder	8
16	Resistor 100k	R_0603_1608Metric_Pad0.98x0.95mm_HandSolder	4
17	Resistor 475	R_0603_1608Metric_Pad0.98x0.95mm_HandSolder	3
18	Resistor 250	R_0603_1608Metric_Pad0.98x0.95mm_HandSolder	2
19	Resistor 330	R_0603_1608Metric_Pad0.98x0.95mm_HandSolder	2
20	Resistor 22k	R_0603_1608Metric_Pad0.98x0.95mm_HandSolder	1
21	Diode RB751CM-40	D_SOD-523_custom	17
22	Ferrite Bead FB	R_0805_2012Metric_Pad1.20x1.40mm_HandSolder	1
23	1:1 SPST Switch TMUX1112	TSSOP-16_4.4x5mm_P0.65mm	4
24	μ C STM32L562ZET6	LQFP-144_20x20mm_P0.5mm	1
25	SPI-EEPROM M95P32-1	SOIC-8_3.9x4.9mm_P1.27mm	1

	Reference	Value	Footprint	Quantity
26	Crystal Oscillator	SG-210STF	SeikoEpson_SG210-4Pin_2.5x2.0mm	1
27	Fuse	ERB-RE1R00V 1A	0603_1608Metric_Pad1.05x0.95mm_HandSolder	1
28	Button Switch	FSM100	SW_PUSH-12mm_custom	3
29	Slide Switch	SW_SPDT	1000-SERIES_SPDT	1
30	Test Point (GND)	TP Keystone 5011	TestPoint_Keystone_5010-5014_Multipurpose	12
31	Test Point	Pin Header	PinHeader_1x01_P2.54mm_Vertical_custom	8
32	OpAmp	TLV9044IPWR	TSSOP-14_4.4x5mm_P0.65mm	3
33	Bridge Rectifier	CDBHD240-G	P21_TO-269AA-MiniDIL	1
34	Battery Charge-Management	MAX8606ETD+T	TDFN-14-1EP_3x3mm_P0.4mm_EP1.78x2.35mm	1
35	LDO	TPS79730DCKRG4	SOT-353_SC-70-5_Handsoldering	1
36	Charge Pump	MAX619CSA+	SO-8_3.9x4.9mm_P1.27mm	1
37	LED (green)	LG_Q396-PS-35	0603_1608Metric_Pad1.05x0.95mm_HandSolder	1
38	LED (red)	LS_Q976-NR-1	0603_1608Metric_Pad1.05x0.95mm_HandSolder	2
39	LED301 (yellow)	LY_L296-P2R1-26	0603_1608Metric_Pad1.05x0.95mm_HandSolder	1
40	LED (blue)	LB_Q39G-N100-35-1	0603_1608Metric_Pad1.05x0.95mm_HandSolder	1
41	Pin Header (2x2)	Pin Header	HDRV4W64P254_2X2_508X508X838P	7
42	Pin Header (2x10)	Pin Header	HDRV20W64P254_2X10_2540X495X838P	6
43	SMA Connector	SMA_Ampheno1_132203-12	SMA_Ampheno1_132203-12_Horizontal_custom	6
44	Pin Header (1x3)	Pin Header	PinHeader_1x03_P2.54mm_Vertical_custom	5
45	Pin Header (2x1)	Pin Header	HDRV2W64P254_2X1_254X508X838P	2
46	Pin Header (2x4)	Pin Header	PinHeader_2x04_P2.54mm_Vertical	1
47	Micro USB Connector	Molex_105164-0001	MOLEX_105164-0001_USB_micro	1
48	Battery Connector	S2B-XH-A(LF)(SN)	JST_S2B-XH-A(LF)(SN)	1
49	JTAG/SWD Connector	FTSH-107-01	FTSH-107-XX-YYY-DV-K-A	1
50	Pin Header (1x14)	Pin Header	PinHeader_1x14_P2.54mm_Vertical_custom	1

	Reference	Value	Footprint	Quantity
51	Pin Header (2x8)	Pin Header	HDRV16W64P254_2X8_2032X495X838P	1
52	Pin Header (2x3)	Pin Header	HDRV6W64P254_2X3_762X508X838P	1
53	Pin Header (2x5)	Pin Header	HDRV10W64P254_2X5_1270X495X838P	1
54	Pin Header (1x8)	Pin Header	PinHeader_1x08_P2.54mm_Vertical_custom	1

^aPlaceholders for matching circuit.

^bFor debugging purposes.

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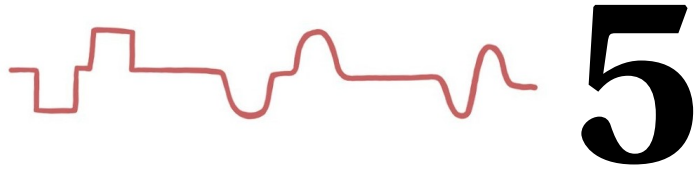
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ON THE EFFICIENCY AND EFFICACY OF STIMULATING WITH NON-RECTANGULAR PULSES

*If you want to accomplish something in the world, idealism is not enough -
you need to choose a method that works to achieve the goal.*

Richard Stallman

Parts of this chapter have been published in the 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC) (2022) [1], ©2022 IEEE. This chapter is a verbatim copy of this paper, with minor changes to comply with the format of this thesis. Reprinted, with permission, from [1]. All research data and code supporting the findings described in this chapter are available in 4TU.ResearchData at <https://doi.org/10.4121/51ddac9e-b096-4b4c-a7b6-87ae11f8f0da>.

5.1. INTRODUCTION

In an attempt to increase stimulation efficacy and simultaneously energy efficiency in neuromodulation applications, recent studies have explored the employment of non-rectangular stimuli. Given these recent findings and while moving towards miniaturised, battery-less, wirelessly-powered systems, the following chapter highlights the importance of an adaptive supply for an output stage with programmable non-rectangular stimuli. Accordingly, after studying different state-of-the-art methods for realising an adaptive voltage supply to adopt a suitable approach for non-rectangular waveforms, it proposes a system-level architecture for multichannel stimulators. In the proposed architecture, a multi-output DC/DC converter (DDC) allows each channel to choose among the available supply levels (i.e., DDC outputs) independently and based on its instant voltage/current requirement. A system-level analysis is carried out in Matlab to calculate the possible energy savings of this solution, compared to the conventional approach with a fixed supply. The energy savings are simulated for a variety of supply levels and waveform amplitudes.

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5.2. ENERGY SAVINGS OF MULTICHANNEL NEUROSTIMULATORS WITH NON-RECTANGULAR CURRENT MODE STIMULI USING MULTIPLE SUPPLY RAILS

To deliver the amount of charge needed for neural activation, neurostimulators typically use either voltage (voltage mode stimulation (VMS)) or current (current mode stimulation (CMS)) controlled pulses. Although VMS benefits from more energy-efficient architectures, it does not allow for sufficient control of the injected charge, given the electrode-tissue interface (ETI) impedance variability. Due to this fact, which impacts safety [2], CMS is preferred in many applications. However, CMS comes at the cost of higher circuit complexity and lower power efficiency at the stimulator output stage, mainly due to the conventional constant supply voltage [3]. The injected current to the tissue is programmed through a current driver powered by this constant supply. This supply should be high enough to fulfil the worst-case scenario, in which the maximum supply level is needed. For scenarios where a smaller supply level would suffice (e.g., the targeted site is easier to activate), any excess voltage drops over the current driver, which leads to unnecessary power dissipation. For multichannel CMS, in particular, if a single constant supply rail is shared among all channels, all channels with a smaller voltage drop across the ETI and tissue are operated sub-optimally. Furthermore, even within a single channel, in the course of a conventional rectangular stimulus, the required compliance will vary over time due to the capacitive-resistive nature of the ETI. These issues have been addressed in the literature by adjusting the supply voltage to the required voltage compliance at the output stage [4–9], or by generating the output current from

de-fluxing an inductor without an intermediate voltage [10].

To increase energy efficiency and stimulation efficacy, recent studies have examined the advantages of non-rectangular waveforms [11]. Non-rectangular waveforms (sinusoidal, triangular, Gaussian, rising, and decaying exponential) have exhibited lower energy requirements for tissue activation, making them more energy-efficient compared to the conventional, rectangular type of stimulation. However, a variation in the programmed stimulation current can be translated to variations in the voltage compliance needed at the output stage. Thus, the opportunity to minimise the losses in output stages with non-rectangular waveforms becomes greater, which is often overlooked in the literature.

5.2.1. ADAPTIVE SUPPLY RAILS FOR NON-RECTANGULAR STIMULI

An increasing number of studies have proposed different methods for adapting the supply level of a stimulator output stage according to its instant voltage and current requirements, to improve its energy efficiency. Fig. 5.1 categorises popular approaches of supply-level adaptation techniques [5–10].

One approach is manipulating the wirelessly received AC signal before or while converting it to a DC supply rail (Fig. 5.1a&b). As illustrated in Fig. 5.1a, the AC power carrier is directly adjusted according to the instant requirement of the stimulation output stages by informing the external device through uplink data communication [7]. Alternatively, adjusting the rectifier's output voltage according to the required compliance voltage at the output stage is proposed [6]. This approach removes the dependency on uplink communication. However, it leads to a less efficient wireless link as the rectifier will reject part of the transmitted energy to the implant.

A more popular approach is to employ a DDC at the implant site to generate the adaptive supply rail(s) out of the constant DC voltage generated by either the wireless link interface or a battery [5], [8], [9], [10]. The proposed DDCs are often based either on inductive buck/boost converters (Fig. 5.1c&d) or switched-capacitor charge pumps (Fig. 5.1e&f). As illustrated in Fig. 5.1c, [8] proposes directly driving the electrodes with an inductive buck-boost converter and controlling it through closed-loop sensing of the ETI's instant voltage and current. Alternatively, in [10] (Fig. 5.1d), an open-loop approach is chosen to charge an inductor with the target current and periodically discharge it to the tissue. While an inductive approach benefits from continuous resolution for generating the voltage and current required at the output stage, it comes at the expense of off-chip inductor(s) and more limited magnetic resonance imaging (MRI) compatibility. Charge-pump circuits ([5],[9]) can benefit from fully-integrated architectures but with a limited resolution for the generated adaptive supplies.

Most supply-level adaptation methods support only one channel at a time by generating a single adaptive supply rail, shared between all channels. Thus, in the case of multiple channels demanding different supply levels simultaneously, either the adaptive circuit needs to be duplicated per channel (Fig. 5.1c), or the supply rail has to adapt to the highest required level, which would not be optimised for other

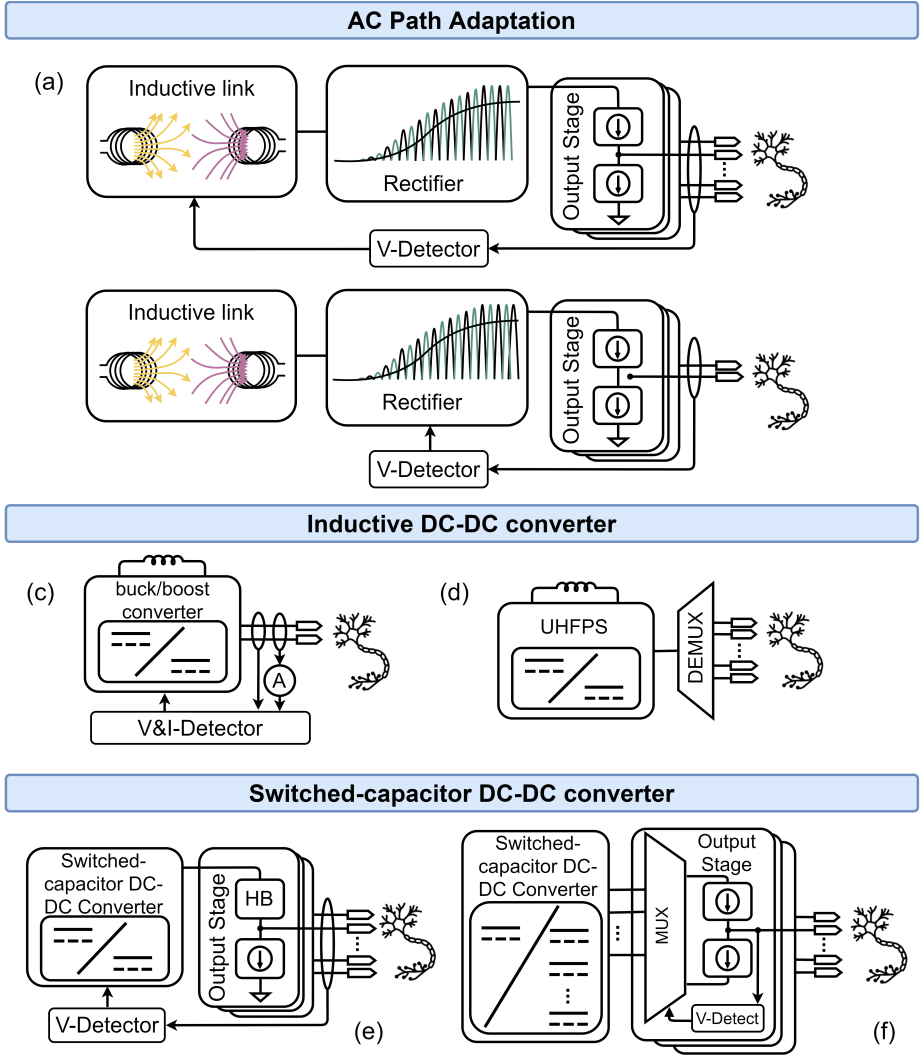


Figure 5.1: State of the art supply-level adaptation techniques with the point of impact on (a) the wireless link, (b) the rectifier, (c-d) the inductive DC/DC converter, and (e-f) the switched capacitor DC-DC converter. In this figure, HB stands for H-Bridge.

channels (Fig. 5.1a&e). To avoid this, [10] has proposed high-frequency interleaving of ultra-high frequency pulsed stimuli (UHFPS) between multiple channels (Fig. 5.1d) at the cost of longer stimulation duration or higher amplitude for the high-frequency pulsed stimuli. Alternatively, a multi-output charge pump has been proposed in [5] (Fig. 5.1f), where each channel connects to one of the charge pump outputs based on its instant voltage/current requirement, independent of other channels.

As illustrated in Fig. 5.2, in the case of non-rectangular stimuli, even channels with

identical waveforms and identical amplitudes may require different instant currents and, consequently, various instant voltage compliances. Therefore, the method proposed in [5] (Fig. 5.1f) is the most suitable approach to be adopted here, as it supports multichannel operation and does not require off-chip components.

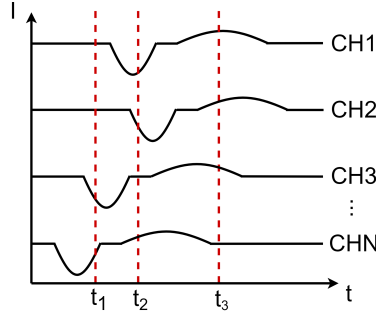


Figure 5.2: Illustration of different instant current requirements for different channels at identical waveforms and amplitudes.

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Here, based on the system of Fig. 5.1f and as a solution against the low efficiency of CMS output stages, a multi-output DDC that enables adaptive and independent supply rails for multiple stimulation channels with non-rectangular waveform stimuli is proposed. Fig. 5.3 demonstrates a generalised architecture of a wireless neurostimulator featuring an energy-efficient output stage capable of programming non-rectangular stimulation waveforms. Moving towards battery-less implanted stimulators to reduce their overall size and avoid risky interventions for a battery replacement, wireless powering of the neurostimulator (using ultrasonic waves, inductive coupling, or RF fields) is preferred in many applications. The received power needs to be rectified and forwarded to a multi-output DDC for generating and sharing multiple DC supply levels for each channel of the output stage to choose from. To appreciate the design tradeoffs for such a multi-output DDC architecture, the following sections present a framework that can be used as a guide for designers to study the energy savings for a variety of parameters and, more importantly, the number of supply rails.

5.2.2. PROPOSED APPROACH AND VALIDATION THROUGH SIMULATION

As mentioned, an adaptive voltage supply at the stimulation output stage can lead to energy savings, especially in the case of a non-rectangular stimulation waveform. Fig. 5.4 illustrates the benefit of an adaptive supply at the example of a half-sine waveform. Here, the voltage supply level is stepped up as soon as the current supply level is not enough to drive the required current and steps down when a smaller supply level suffices. To calculate the energy savings from using an adaptive supply compared to a constant supply, we need to consider the energy (E) required to generate a single pulse over the period T for both cases. This energy is expressed as

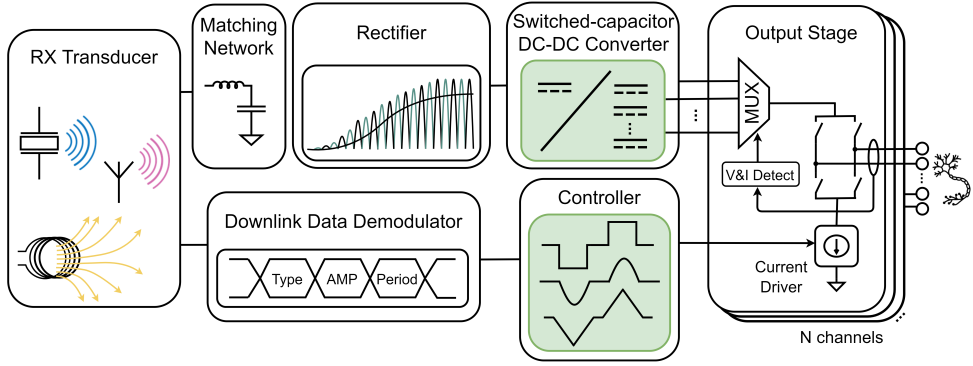


Figure 5.3: High-level block diagram of a complete wirelessly-powered implantable device. The wirelessly received power is rectified and received by the proposed switched capacitor DC-DC converter to generate the 6 (depending on the application) DDC outputs to provide for the stimulation output stage. In each output stage, the proper DDC output is chosen using an HV-MUX according to the electrode's monitored voltage and/or current level. Biphasic stimulation is possible with an H-bridge.

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a function of the power (P) needed to supply said pulse:

$$E(t) = \int_0^T P(t) dt \quad (5.1)$$

For an ideal (also adiabatic [8]) power supply, where the supply follows the needed voltage for stimulation through an infinite number of supply steps, and considering a purely resistive load at the ETI, the power required for one pulse is

$$P(t) = I(t) \cdot V(t) = I^2(t) \cdot R, \quad (5.2)$$

where $V = I \cdot R$. However, for a realistic load representation, the capacitive nature of the ETI needs to be considered as well. In this case, the voltage compliance varies according to the capacitive value of the ETI and the injected charge (Q), leading to the following power consumption when assuming a conventional constant voltage supply:

$$P_{\text{const}}(t) = I(t) \cdot V_{\text{max}}, \quad V_{\text{max}} = \max \left(I(t) \cdot R + \frac{Q(t)}{C} \right) \quad (5.3)$$

The effect of the capacitive nature of the ETI is visible at the end of the pulse (Fig. 5.4, bottom right corner of inset). Because of the accumulated charge on the ETI's double-layer capacitor, the voltage does not return to zero. This effect depends strongly on the capacitive value of the ETI, in relation to its real part. In this case, the effect is not that strong, given the chosen values.

In the case of an adaptive power supply, the power is calculated based on the instantaneous voltage needed at the different levels ($V_{\text{quantized}}$), as in:

$$P_{\text{adapt}}(t) = I(t) \cdot V_{\text{quant}}(t) = I(t) \cdot \left(I_{\text{quant}}(t) \cdot R + \frac{Q(t)}{C} \right) \quad (5.4)$$

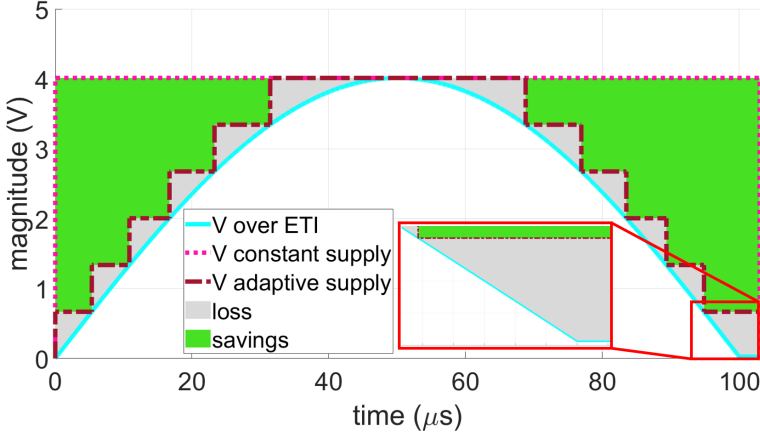


Figure 5.4: Voltage over the ETI (RC-load with $R_S = 1 \text{ k}\Omega$, $C_{DL} = 10 \text{ }\mu\text{F}$) for a half-sine wave at the maximum amplitude (4 mA) and the maximum number of available DDC outputs (6), for an ideal (adiabatic) supply (solid cyan line), for a constant supply (dotted pink line), and for an adaptive supply (dashed purple line). For an amplitude $< \text{max}$, the number of supply rails decreases, thus increasing the system's relative energy savings.

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The energy savings (E_{save}) between the two scenarios (adaptive vs. constant supply) are expressed with a percentage (%) and calculated as:

$$E_{\text{save}} = (1 - E_{\text{adapt}}/E_{\text{const}}) \cdot 100\%. \quad (5.5)$$

A high-level numerical investigation has been implemented using Matlab to calculate the possible energy savings when comparing an adaptive power supply to the conventional approach. For this analysis, a capacitive-resistive (RC) load of $1 \text{ k}\Omega$ in series with $10 \text{ }\mu\text{F}$ is assumed, based on the typical range of deep brain stimulation (DBS) electrodes used in human patients [12]. Different monophasic stimulation waveforms (half-sine, Gaussian, triangular) are evaluated, with a pulse width of $100 \text{ }\mu\text{s}$, and with stimuli amplitudes ranging from $250 \text{ }\mu\text{A}$ to 4 mA , with steps of $250 \text{ }\mu\text{A}$. The energy savings have been calculated for different numbers of equally separated supply rails, ranging from 2 to 6 steps. This provides an insight into the needed number of supply rails and the energy savings for a specific waveform. It should be noted that this calculation acts as a practical example. An adaptation to any impedance and amplitude combination is possible.

5.3. RESULTS & DISCUSSION

Fig. 5.5 illustrates the power consumption for a constant supply, an adaptive supply with 6 DDC outputs, and an ideal (adiabatic) supply for the example of a half-sine stimulation pulse while considering the capacitive nature of the ETI ($R_S = 1 \text{ k}\Omega$, $C_{DL} = 10 \text{ }\mu\text{F}$). In the ideal supply case, the voltage supplied is equal to the demand of each stimulus waveform, resulting in very little power loss, coming from the small

voltage overhead needed for the current driver (not visible here). The green shaded area illustrates the energy savings when employing the proposed adaptive supply compared to a conventional constant supply.

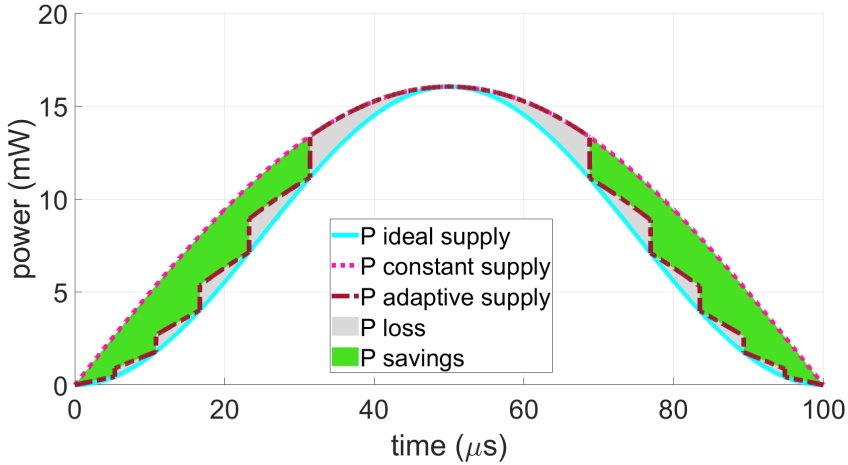


Figure 5.5: Power consumption for a half-sine wave (RC -load with $R_S = 1 \text{ k}\Omega$, $C_{DL} = 10 \text{ }\mu\text{F}$) at the maximum amplitude (4 mA) and the maximum number of available DDC outputs (6), for an ideal (adiabatic) supply (solid cyan line), for a constant supply (dotted pink line), and for an adaptive supply (dashed purple line). The energy savings of the adaptive supply compared to the conventional supply are visualised in green.

Fig. 5.6 demonstrates the energy savings for a half-sine, with a pulse width of $100 \text{ }\mu\text{s}$, stimuli of different amplitudes, and different numbers of uniformly distributed supply rails. Energy savings of up to 83% are possible when employing 6 supply rails, at the lowest examined amplitude ($250 \text{ }\mu\text{A}$). Similar energy savings were calculated for a Gaussian and a triangular waveform, and the results are summarised in Table 5.1. By decreasing the number of supply rails, the total possible energy savings decrease. This is also the case for larger amplitudes, resulting in a larger needed voltage compliance. For a full-scale (here 4 mA) half-sine, the energy savings reach up to 15%, for a Gaussian up to 22%, and for a triangular waveform up to 26%, when using 6 DDC outputs.

The energy savings calculated here are higher for smaller stimulus amplitudes since lower voltage supplies would suffice to generate the pulses. A higher number of supply levels also leads to higher savings. However, the relative increase in energy saving does not respectively increase with the number of supply levels. It can be seen from Fig. 5.6 that the energy savings for 5 and 6 supply rails are comparable. Given the increase in circuit and wiring complexity when increasing the number of supply levels, a trade-off can be made between the number of supply rails and the amount of energy saved.

The proposed approach can be advantageous for multichannel applications with different supply needs for every channel. It allows each stimulation channel to

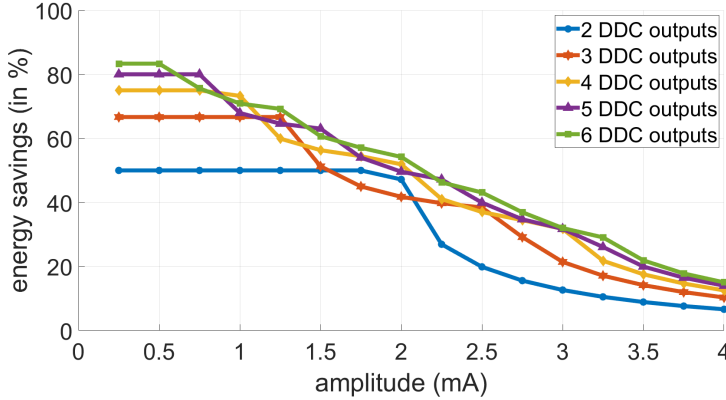


Figure 5.6: Energy savings of a half-sine wave (RC-load with $R_S = 1 \text{ k}\Omega$, $C_{DL} = 10 \text{ }\mu\text{F}$), for stimulus amplitudes varying between $250 \text{ }\mu\text{A}$ and 4 mA , and for 2-6 uniformly distributed DDC outputs.

Table 5.1: Energy savings in % of multiple supply rails vs. a constant supply for different waveform types, when employing up to 6 DDC outputs.

	Half-Sine		Gaussian		Triangular	
# of DDC outputs	Full scale ^a	Min amp ^b	Full scale	Min amp	Full scale	Min amp
2	7	50	12	50	13	50
3	10	67	17	67	19	67
4	13	75	20	75	22	75
5	14	80	21	80	24	80
6	15	83	22	83	26	83

^a In the full-scale supply, all 6 DDC outputs are employed.

^b Min amp (minimum amplitude) is equal to 1/16 of the full-scale supply ($250 \text{ }\mu\text{A}$).

connect to the pre-generated supply rails based on its instant need and independent of other channels. Furthermore, it can benefit multichannel applications with different electrode sizes at every channel. In such a case, the voltage compliance needs per channel might differ significantly. This approach would allow each stimulation channel to connect to the most suitable pre-generated supply rail.

5.4. CONCLUSION

This chapter highlights the importance of employing an adaptive voltage supply to power a stimulation output stage with programmable non-rectangular stimulus waveforms and presents the possibility of gaining high energy savings when compared to a conventional constant supply. Simulations for the particular indicative case revealed energy savings between 7% and 83%, depending on the type of waveform, the number of supply levels and the stimulus amplitude. The maximum energy savings of up to 83% result when employing 6 DDC outputs and the lowest current amplitude explored ($250\mu\text{A}$), and can be as high as 26% for a full-scale amplitude (4mA). The proposed approach offers the potential for full system integration, without off-chip components, for a system aiming at higher overall efficiency and smaller silicon area.

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CONCLUSION & RECOMMENDATIONS FOR FUTURE WORK

*Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more, so that we may fear less.*

Marie Curie

6.1. CONCLUSION

This thesis provided accessible and affordable designs to address the needs of increased complexity and functionality in neuromodulation hardware. Mainly on the basis of two different applications, dorsal root ganglion (DRG) stimulation and vagus nerve stimulation (VNS), two different systems were developed to fulfil the individual requirements of each application. Both systems were built using commercially available components, for ease of reproducibility by other research labs and to facilitate their use in an experimental (preclinical or clinical) environment. Throughout their design process, aspects like multichannel stimulation, power-efficiency, increased stimulation selectivity and stimulation safety were investigated and implemented. These designs aid in further exploring the potential of neuromodulation applications, including but not limited to DRG stimulation and VNS.

CHAPTER 3

Chapter 3 presented the design and development of a DRG stimulator system intended for use in early clinical trials for motor recovery after spinal cord injury (SCI). The system was built using commercially available components and supports independent control of multisite/multilevel bilateral (on both sides of the spinal cord) stimulation through 16 independently controllable channels. It can supply output currents of up to 25.4 mA, and pulse sequences similar to actual locomotion patterns. In the attempt to increase the safety of this and similar neurostimulator devices, given the direct contact with the neural tissue of the patient, a charge balancing system was designed to be used as an add-on for neural stimulators. The charge balancing system is suitable for a broad range of frequencies up to the kilohertz domain. It continuously monitors the offset voltage buildup at the electrode site and applies a corrective current to compensate for the charge accumulation that leads to this voltage buildup, reducing it to values as low as 0.7 mV.

CHAPTER 4

Chapter 4 presented the design and development of an ultrasonically powered neuromodulation platform to explore the potential that recent neuroscientific advancements have identified in VNS. The platform serves as a practical and versatile experimental tool, using only off-the-shelf components, making it easily reproducible by other research labs. The platform can perform both neural activity excitation and inhibition, allowing for further investigation of spatially and directionally selective stimulation. It stimulates the tissue using voltage-controlled biphasic and monophasic pulses, with pulse widths varying between 0 and 1500 μ s, and a pulse repetition rate (PRR) between 1 Hz and 1 kHz for neural excitation and 1 kHz to 50 kHz for inhibition. Furthermore, it supports a connection to 6 electrodes for excitation and 2 for inhibition. To enhance stimulation safety, it includes a charge balancing mechanism based on a digital PID controller, reducing the offset voltage between the stimulating electrodes down to 2 mV. Working towards a miniaturised

version and to increase energy efficiency, the same signal used for powering the platform is also used for neural stimulation. This eliminates the need for an additional voltage or current source.

CHAPTER 5

Chapter 5 investigates the energy savings of an adaptive supply integrated into a system that offers programmable non-rectangular stimulation pulses and proposes a system-level architecture for multichannel stimulators. In this architecture, through the use of a multi-output DC/DC Converter, each channel can choose among the 6 available supply levels, based on its individual and instant voltage/current requirement. A system-level analysis carried out in Matlab estimates the possible energy savings of the proposed adaptive supply when compared to the conventional approach with a fixed supply, yielding energy savings as high as 83%, an essential factor to consider when working towards low-power devices.

6.2. RECOMMENDATIONS FOR FUTURE WORK

MINIATURISATION

The devices implemented in Chapters 3 and 4 were prototypes aiding in identifying the required components that fulfil the functionality needs of the intended applications. Before directly moving towards an implantable version, they both have the potential of being designed with a smaller form factor while maintaining their benchtop configuration. Going one step further, and as soon as all relevant physiological parameters and responses are identified and analysed, the two systems can be implemented in a fully miniaturised and implantable version. This will require the development of a low-power system that can support wireless power transfer and communication.

WIRELESS POWER TRANSFER USING INTEGRATED TRANSDUCERS

The neuromodulation platform presented in Chapter 4 can be powered wirelessly using acoustic waves, with the signal used for powering also used for neural stimulation. To verify this functionality, commercially available transducers were used as receivers. Designing towards an implantable version requires the replacement of the bulky commercial transducers with small, integrated transducers, such as piezoelectric or capacitive micromachined ultrasound transducers (PMUTs or CMUTs, respectively) [1, 2]. Attempts were made during the thesis to power the device using CMUTs as receivers; however, they did not manage to provide the necessary amount of power. To ensure that the transferred energy will suffice to power the device, the design needs to be further optimised in terms of energy efficiency and include only the most essential components.

WIRELESS COMMUNICATION

The device in Chapter 3 communicates wirelessly via Bluetooth to a GUI on a laptop, while the device in Chapter 4 does not support wireless communication and rather needs a USB connection to update its stimulation parameters through the GUI. While Bluetooth is a successful means of data transfer, it lacks in security, an aspect that is becoming increasingly important in the development and use of neural implants [3, 4], calling for alternative ways of uplink and downlink communication. In contrast to the omnidirectional electromagnetic waves, as emitted in the case of communication with Wi-Fi or Bluetooth, ultrasound is highly targeted and has a short range for frequencies above 1 MHz [4]. This makes eavesdropping or injecting malicious messages into the implant extremely difficult, deeming ultrasound an ideal candidate for wireless communication [4]; a feature that can be combined with the capacity of acoustic waves to transfer power to the implant. Integrating wireless communication through ultrasound in the developed designs will therefore enhance their security while allowing for greater implantation depths [5].

MICROCONTROLLER UNIT CHOICE

Improving the overall energy efficiency of the system will involve, amongst other design choices, a suitable choice for a microcontroller to provide the processing unit for the developed neural implant. Using a microcontroller for this task instead of a custom-built digital unit allows for a lower-cost and universally accessible solution. The ultra-low-power microcontroller STM32L562 used in the design of the neuromodulation platform presented in Chapter 4 is used to generate the stimulation pulses through its advanced timers, as well as to implement the charge balancing mechanism that enhances the system's safety. Although the chosen microcontroller series offered the most advanced power-saving capabilities at the time, since then, new series have been released (STM32U5), promising even greater power-saving potential. By choosing an ultra-low-power microcontroller with the appropriate packaging, its power needs and size can be reduced to a minimum, thus greatly reducing the power needs of the whole system as well as increasing its miniaturisation potential. Furthermore, by optimising the microcontroller software, its power consumption can be reduced from mA to μ A. Finally, choosing a microcontroller with a higher number of advanced timers will allow for the independent control of a larger number of electrodes, providing for a higher degree of spatial selectivity.

ADAPTIVE POWER SUPPLY IMPLEMENTATION

Chapter 5 introduces a novel system-level architecture for multichannel stimulators that support the output of programmable non-rectangular stimulation pulses and validates the increase in efficiency that the proposed design can achieve. With the validation only relying on simulations, the next step should be implementing this design with appropriate components and integrating it into a stimulator. That way, the effectiveness of the design in increasing the energy savings can be validated under more realistic conditions.

INTEGRATION OF PHYSIOLOGICAL RECORDING

The recording of physiological signals is becoming an integral component for the development of closed-loop stimulation. By introducing recording at the stimulation site in the neuromodulation platform presented in Chapter 4, the intended effect on the neural cells can be directly verified, for both neural activity excitation and inhibition. The monitoring of the induced neural activity is especially interesting in this particular design, given that the amplitude of the stimulation pulses is dictated by the harvested ultrasound used for powering, since the signal used for powering is also the signal used for stimulation. Should the available power not suffice to stimulate the nerve, due to fluctuations of the harvested ultrasound affecting the pulse amplitude, a direct feedback from the nerve will notify the user and prompt them to adapt the stimulation settings.

IN VIVO VALIDATION

The developed stimulators in Chapters 3 and 4 were both validated in a phosphate-buffered saline (PBS) solution that emulates the environment of the inner body. While this provides an initial impression of how both systems would perform when in contact with actual tissue, an in vivo validation of their functionality would confirm their effectiveness and verify their success in their respective intended use.

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Και τα παρτάλια οι σκέψεις μας
Πειρατική σημαία
Όλα στραβά γινήκανε
Και όλα είν' ωραία

Θανάσης Παπακωνσταντίνου: Σιμόν

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CURRICULUM VITÆ

Konstantina KOLOVOU KOURI

EDUCATION

- | | |
|------------|--|
| 2010–2016 | Bachelor of Science in Electrical Engineering
Technische Universität Berlin, Germany |
| 2016–2019 | Master of Science in Biomedical Engineering
Technische Universität Berlin, Germany |
| 2019–2025 | PhD degree in Microelectronics
Technische Universiteit Delft, the Netherlands
<i>Thesis:</i> Designing Accessible Hardware for Electrical Neuro-
modulation Applications
<i>Promoters:</i> Dr. V. Giagka and Prof. Dr. Ir. W. A. Serdijn |
| 2019–today | Research Assistant
Fraunhofer Institute for Reliability and Microintegration (IZM),
Berlin, Germany |

SHORT BIO

Konstantina Kolovou Kouri, born in Athens, Greece, in 1992, is currently employed at the Fraunhofer Institute for Reliability and Microintegration (IZM) in Berlin, Germany. She acquired her Bachelor's degree in Electrical Engineering, with a specialisation in Electronics and Information Technology, from the Technical University of Berlin (TU Berlin), in Germany, followed by a Master's degree in Biomedical Engineering, also from the TU Berlin. In 2017, she started working for Fraunhofer IZM as a student assistant, and continued working there as a research assistant from 2019, while simultaneously pursuing a PhD at the Delft University of Technology (TU Delft), in the Netherlands. Since 2023, she has held a full-time position as a research assistant at Fraunhofer IZM, in the department of System Integration and Interconnection Technologies. Her main research interests include the hardware design of versatile neurostimulators, focusing on high efficiency and low power consumption, while examining the potential of energy harvesting and wireless power transfer through ultrasound.

LIST OF PUBLICATIONS

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- K. **Kolovou-Kouri**, L. Holzapfel, D. Ferreira Dias, L. Meixner, W. A. Serdijn, and V. Giagka. “Ultrasonically Powered Neuromodulation Platform Intended for Spatially and Directionally Selective Electrical Stimulation”. In revision. Preprint on: <https://doi.org/10.1101/2025.05.07.652395>

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POSTERS AND PRESENTATIONS

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