Selective Peripheral Nerve Interfaces

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PhD Thesis by

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Preface

The work presented in this thesis was carried out during my employment as PhD student from 2008 to 2010 at the Center for Sensory Motor Interaction, Department of Health Science and Technology, Aalborg University. The work was financed by the Danish National Advanced Technology Foundation (J.005-2005-1) and would not have been possible without the help and guidance of a number of people to whom I am truly grateful.

First of all I am indebted to my supervisor Johannes J. Struijk for his great ideas and guidance and always providing constructive feedback and fruitful discussions of key issues. The co-authors of the papers of this thesis, Cristian Sevcencu and Mathijs Kurstjens, provided great help with especially the laboratory preparations, which were essential since I had no prior experience with building nerve electrodes or doing animal experiments. The employees at the animal lab, Department of Pathology, Aalborg Hospital, and especially Torben Madsen, Ole Sørensen, and Jens Sørensen, provided essential support with animal handling and preparation and were always ready to discuss the latest football results during coffee breaks.

Furthermore, my colleagues at the Neural Interface and Prostheses Laboratory provided fruitful discussions of both my particular work and the whole area in general. Finally, I want to thank all the colleagues at the Department for Health Science and Technology for creating a great work environment.

English summary

Neural devices that are implanted in the body to interface peripheral nerves are a promising technology for treatment of a number of disorders. Muscles may e.g. be activated by nerve stimulation to regain lost function after spinal cord injury or stroke, bladder spasms can be suppressed and sphincter muscles contracted to restore continence, epileptic seizures may be averted, and the nerve activity that would have controlled the muscles of the natural hand could be used to control an artificial prosthesis in amputees. The electrodes, which constitute the interface between the nerve and the electronic system, play a key role in the development of these systems because they determine the nature of interaction and sets out the limitations of the neural prosthetic device. It is desirable for the interface to provide the highest possible selectivity because nerve fibers can be organized in functional groups within the nerve so that, e.g., multiple muscles may be individually controlled by selective activation of subareas of the same nerve. However, the implantation of electrodes comes with a risk of damage to the nerve, a risk that should not exceed the expected gain. The selectivity must therefore be optimized without substantial increase in invasiveness. In this respect the perineurium constitutes an important boundary; electrodes that leave the perineurium intact can be considered relatively safe if care is taken to avoid compressive forces to the nerve and proper materials are used, whereas electrodes that penetrate the perineurium leave the nerve fibers less protected and therefore involve a higher risk.

In this thesis, three studies were conducted to investigate extra-fascicular selectivity. In study I, the stimulation selectivity of the transverse tripolar configuration was investigated with cuff electrodes in the sciatic nerve of nine rabbits. The transverse tripolar configuration achieved excellent selectivity in recruiting the small cutaneous and medium-sized peroneal nerve branch (0.98±0.01 and 0.95±0.08 mean±SD, respectively), but failed to recruit the large tibial branch selectively. The transverse tripolar configuration could thus provide selective activation of small and medium sized superficial fascicles of a nerve, while other configurations need to be used for recruiting other fascicles. In study II, a novel interfascicular interface was presented and basic stimulation properties were tested in the sciatic nerve of nine rabbits. The interfascicular interface was easily implanted in the nerve and achieved excellent selectivity in recruiting the tibial vs. peroneal nerve branch (0.98±0.03). In study III, the recording selectivity of the interfascicular interface was tested and monopolar, bipolar, and tripolar stimulation configurations were compared in the sciatic nerve of 10 rabbits. All stimulation configurations achieved excellent selectivity (0.98) without any significant differences among the configurations, but the longitudinal bipolar configuration required the lowest stimulation amplitude. The monopolar averaged reference configuration achieved a recording selectivity ratio of 4.13±0.92, which is promising compared to the 1.4 obtained by cuff electrodes under similar conditions.

Interfascicular electrodes could be an interesting addition to the interfaces available for selective stimulation and recording of peripheral nerves and the transverse tripolar configuration could, along with other field shaping methods, improve the stimulation selectivity of cuff electrodes and other nerve interfaces. More studies are, however, required to develop a biocompatible interfascicular interface and test its stability and safety in chronic experiments. Furthermore, interfascicular selectivity should be evaluated in a polyfascicular nerve.

Dansk resumé

Neurale apparater, som er implanteret i kroppen, er en lovende teknologi til behandling af en række lidelser. Muskler kan fx aktiveres af nervestimulation for at genvinde tabt funktion efter rygmarvsskade eller slagtilfælde, blærespasmer kan undertrykkes, ringmuskler sammentrækkes for at genoprette kontinens, epileptiske anfald kan undertrykkes og den nerveaktivitet, som ellers ville have styret musklerne til en amputeret hånd, kan i stedet bruges til at kontrollere en kunstig håndprotese. Elektroderne, som udgør grænsefladen mellem nerven og det elektroniske system, spiller en afgørende rolle i udviklingen af disse systemer, fordi de afgør, hvilken type interaktion, der er mulig, og udstikker implantatets begrænsninger. Det er ønskværdigt at opnå den højst mulige selektivitet, da nervefibrene kan være organiseret i funktionelle grupper i nerven, så fx flere muskler kan kontrolleres individuelt med selektiv aktivering af underområder af den samme nerve. Implantation af disse elektroder i kroppen medfører imidlertid en risiko for nerveskade, og denne risiko må ikke overstige det forventede udbytte ved behandlingen. Selektiviteten skal derfor optimeres uden at den risiko, der er involveret i implanteringen, øges væsentligt. I denne forbindelse udgør perineuriumet, som omgiver bundterne af nervefibre i nerven, en vigtig grænseflade: Elektroder, som er placeret uden for perineuriumet, kan betragtes som relativt ufarlige, hvis de designes med omhu, så kompression af nerven undgås og de rigtige materialer anvendes. Elektroder, som trænger igennem perineuriumet, udgør derimod en større risiko, da de kommer i direkte kontakt med de ubeskyttede nervefibre.

I denne afhandling er der udført tre studier for at undersøge ekstra-fasciculær selektivitet. Studie I undersøgte selektiviteten af den tværgående tripolære konfiguration med manchet-elektroder i ischiaticus nerven i ni kaniner. Den tværgående tripolære konfiguration opnåede fremragende selektivitet i rekruttering af den lille kutane, og den mellemstore peroneale, nerveafgrening (hhv. 0,98±0,01 og 0,95±0,08 middel±SD), men var ikke i stand til at rekruttere den store tibiale afgrening selektivt. Den tværgående tripolære konfiguration kunne således anvendes til selektiv aktivering af små og mellemstore nervebundter i yderkanten af nerverne, mens andre konfigurationer er nødvendige for at aktivere de øvrige nervebundter. Studie II præsenterede en ny interfasciculær elektrodetype og undersøgte dens basale stimulationsegenskaber i ischiaticus nerven i ni kaniner. Elektroden var nem at implantere og opnåede fremragende selektivitet i rekrutteringen af hhv. den tibiale og den peroneale nerveafgrening (0,98±0,03). Studie III undersøgte den interfasciculære elektrodes evne til selektivt at optage nervesignaler og sammenlignede monopolære, bipolære og tripolære stimulationskonfigurationer i ischiaticus nerven i 10 kaniner. Alle stimulationskonfigurationer opnåede fremragende selektivitet (0,98) uden signifikante forskelle mellem konfigurationerne, men den longitudinale bipolære konfiguration krævede den laveste stimulationsamplitude. Den interfasciculære

elektrode opnåede en selektivitetsratio på op til 4,13±0,92 i optagelse af nerveaktivitet, hvilket er lovende sammenlignet med manchetelektroder, som opnåede en ratio på 1,4 under tilsvarende forsøg.

Interfasciculære elektroder kunne være en interessant tilføjelse til de nerveelektroder, som er tilgængelige for selektiv stimulation og optagelse fra perifere nerver, og den tværgående tripolære konfiguration kunne, sammen med andre metoder til at styre stimulationsfeltet, forbedre stimulationsselektiviteten af manchetelektroder og andre nerveelektroder. Der kræves dog flere studier med henblik på at udvikle en biokompatibel interfasciculær elektrode og teste dens stabilitet og sikkerhed i kroniske studier. Selektiviteten af den interfasciculære elektrode bør desuden undersøges i større nerver.

Chapter 1.

Introduction

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1.1 INTRODUCTION

Historically, the development of neurostimulation has been closely tied to the advances in technology and knowledge of electricity, which is natural since the nervous system provided the best sensor for electrical activity prior to the advent of modern sensing technologies. Natural sources of electrical energy, i.e. minerals, metals, and animals, were used for electrotherapy in many ancient cultures, possibly dating as far back as 9000 BCE [1, 2]. Topedo fish and electric eel was used for the treatment of headace, gout, melancholy, migraine, and epilepsy, throughout the Middle Ages in concordance with “Compositiones” (47 CE) by the roman physician Scribonius Lagus [2]. The development of electrical technology and understanding accelerated in the 18th century with the invention of new electrical sources, e.g., the capacitor by Von Kleist and Musschenbroek in 1745, the battery by Volta in 1790, and the alternating current generator by Faraday in 1831 [1, 2]. The study of electro-neurophysiology was initiated by Galvani’s experiment eliciting muscle contractions in frogs, published in 1791, and expanded by others stimulating both peripheral nerves and the brain to elicit muscle contractions in animals and humans [1, 2]. Electrotherapeutic treatments were developed along with the advances in technology and knowledge of electricity and neurophysiology for various neurological disorders during the 19th century. The development of treatments for various disorders has continued to profit from the development in technology as well as the increase in physiological understanding with e.g. the development of methods of microfabrication and microelectronics in the latter half of the 20th century enabling fully implantable devices for chronic neuromodulation. Electrical or magnetic stimulation of neural tissues of the brain, spinal cord, or peripheral nerves can today be applied from inside or outside the body to treat patients with a wide range of disorders either during short-term training sessions for rehabilitation or chronically in patients that cannot attain the desired functional gain by neuroplasticity [2-4]. This thesis, however, focus exclusively on the interaction with the peripheral nervous system.

Peripheral nerves connect the central nervous system to the body and enable it to control the function of organs and provide it with information from sensory organs throughout the body. Peripheral nerves thus provide an interface both for exerting control on peripheral organs, such as muscles, and for modulating information to the central nervous system. Since the peripheral nerves remain functional after injury to the central nervous system, i.e. stroke or spinal cord injury, has caused a loss of function in patients there has long been an interest in artificially activating the nerves by means of functional electrical stimulation to regain lost function, especially in the form of direct or indirect muscle activation. In some cases, the patients may regain lost function through neural plasticity and only need the stimulation during training sessions to facilitate more rapid progress or otherwise improve the rehabilitation. Some patients are, however, not capable of regaining the lost function and require continuous treatment throughout the rest of their lives by means of a portable stimulation system, which they can easily carry on their bodies while coping with daily activities. The first of these portable systems, called neural prosthetic devices, that was developed was a system by Liberson and colleagues for correction of drop-foot by transcutaneous stimulation of the common peroneal nerve in timing with the gait cycle [5].

While surface mounted systems are useful for functional electrical stimulation in rehabilitation they do, however, have numerous limitations when used in a neural prosthesis. These include that they require daily setup, which can be cumbersome and may result in variations in electrode placement that complicates the control algorithms, the transcutaneous currents are unpleasant at best and can be painful, the external parts, i.e. lead wires and stimulation and control apparatus, are unaesthetic and may be cumbersome to wear, the nerve selectivity and thereby the degree of control is low, and only superficial nerves can be stimulated. There has therefore long been a focus on developing neural prosthetic devices that are partly or fully implantable. Such systems are already available for clinical use for life-sustaining ventilator assistance, treatment of incontinence, treatment of drop-foot, suppression of epileptic seizures, and alleviation of pain [6-22]. In addition to these accepted treatments, peripheral nerve stimulation could be used to help patients with a number of other disorders, e.g. cardiac risk, depression, and obesity [23-29]. Implanting electrodes on, or even inside, peripheral nerves furthermore have the advantage that it is possible to record naturally occurring activity from the nerves. Using information from nerve recordings could improve functional electrical stimulation by alleviating the need for external components to provide trigger information for the stimulation, enable closed-loop stimulation where no triggers can otherwise be obtained, and provide even more applications for neural prosthetic devices, e.g. control of a mechanical prosthesis [30-46].

In the following sections nerve anatomy and the selectivity of peripheral nerve electrodes are discussed and some of the most commonly applied implantable nerve electrodes are presented before the problem area of the project is finally defined.

1.2 PERIPHERAL NERVE STRUCTURE

Peripheral nerves consist of 0.2-3.0 μm diameter unmyelinated and 2-25 μm diameter myelinated nerve fibers, or axons, which are collected in groups of 0.4-3.0 mm diameter called fascicles [47]. A nerve may contain a single (monofascicular), a few (oligofascicular), or many (polyfascicular) fascicles (see Figure 1.1) [47, 48]. In polyfascicular nerves the fascicles may be further organized in fascicle groups within the nerve [47]. The nerve fibers and endoneurium of the fascicles are contained within a tough sheath of perineurial cells and collagen fibers around each fascicle called the perineurium. The fascicles are held together by epineurial connective tissue that can be subdivided in loose internal, or epifascicular, epineurium between the fascicles and a hard sheath around the nerve of external, or epineurial, epineurium [48].

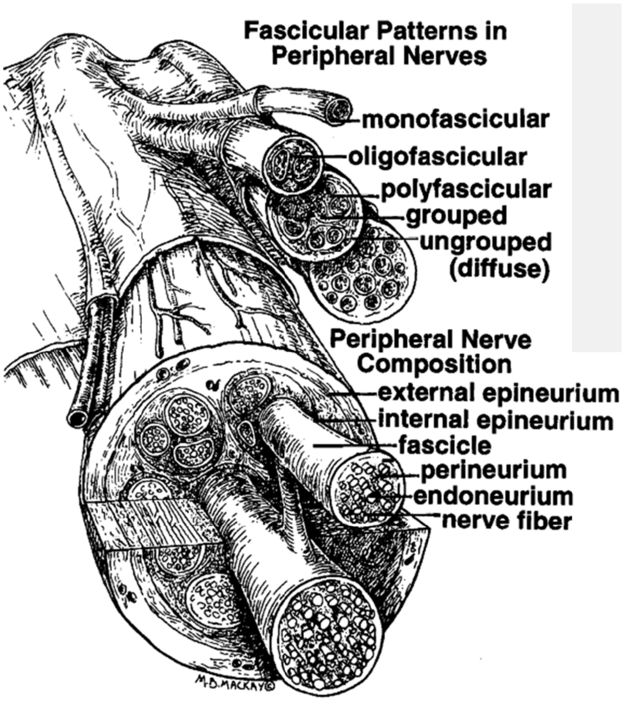

Figure 1.1. Illustration of the structure of peripheral nerves. [47]

Nerves are often bidirectional, containing both efferent, e.g. motor, fibers and afferent, e.g. sensory, fibers and are typically arranged in a way so that the most proximal peripheral nerves can be rather large, but as they are followed distally they branch out and dissipate into smaller nerves to innervate various structures along the way [48]. The nerves were initially thought to be organized in a cable-like manner in which fibers innervating a particular structure, e.g. a muscle, would remain together in the same fascicle throughout the nerve, but are now known to have a more complex structure in which fascicles mix, combine, and split along the length of a nerve [48]. The nerves do, however, have a somatotopic organization close to branching points, so that fibers of one branch will continue to be separated from fibers of the other branches immediately proximal to branching point while fascicles intermingle at more proximal levels of the nerve [48-51]. Despite this proximal regrouping of fibers, axons related to a specific area may even retain their somatotopic organization at very proximal levels of the nerve, although such organization may depend on nerve and species [48].

1.3 SELECTIVITY OF PERIPHERAL ELECTRODES

Depending on e.g. the location of the electrodes, selectivity can both refer to the ability to stimulate a single nerve without also activating other tissues and the ability to interface only a subset of the fibers within a nerve. In the following I will focus on within-nerve selectivity. Due to the nerve composition described in section 1.2 the ability to interface nerves in a selective manner can be very useful, as it may enable a single interface to access multiple, functionally distinct, groups of fibers. The selectivity of nerve interfaces can be split into three main categories; 1) topological selectivity, 2) direction selectivity and 3) fiber type selectivity. Because of the somatotopic organization of peripheral nerves, the ability to selectively interface topological distinct areas of the nerves is equivalent to interfacing anatomically distinct areas, e.g. different muscles, and can thus enable a single nerve implant to replace implants on multiple more distal nerves, thereby reducing surgical complexity. The ability to confine stimulation to one direction can enable, e.g. precise control of specific muscles without undesired sensation or reflex interference or vice versa. Selective recording of unidirectional axon potentials of a specific fiber type may also provide the means of e.g. accessing specific types of sensory information.

While the usefulness of selective interfaces is apparent selecting a method for assessing selectivity is less straightforward. Furthermore, there is a major difference between stimulation selectivity and recording selectivity; for stimulation, topological selectivity is related to shaping the current field in a way that e.g. creates a strong field gradient in the target area without current spillover to non-target areas of the nerve, while recording selectivity is related to cross-talk where both non-target sources within the nerve and sources outside of the nerve can be regarded as noise interference in the recorded signal.

1.3.1 Stimulation selectivity

Several approaches have been employed to evaluate topological stimulation selectivity, which typically focus on fascicle-level selectivity. The Cleveland group has developed a stereotaxic frame for measuring 3D joint forces elicited by stimulation in the hind limbs of anaesthetized cats and analyzes joint torque vectors to evaluate independent activation of functional groups [52]. The selectivity evaluation is, however, usually based on either muscle activation, which can be measured in the form of force or electromyographic (EMG) signals recorded from muscles, which are innervated by the stimulated nerve, or electroneugraphic (ENG) signals measured from branches of the nerve [53-59]. Selectivity is typically defined as the activation of the target structure divided by the sum of activation in all structures, i.e. as the proportion of total activation occurring in the target structure. To compensate for the differences in e.g. size and fiber composition of the nerves or muscles all evoked potentials are first normalized to a fraction, f, of full recruitment by dividing with the maximum response recorded on the same structure. Based on this fraction, the selectivity (S) in recruitment of a branch or muscle (b) can then be defined as

$$S_b(I) = \frac{f_b(I)}{\sum_{i=1}^{N} f_i(I)} \tag{1.1}$$

where N is the number of recorded nerve branches or muscles and I is the stimulation intensity [53-58]. However, a drawback of this definition is that the resulting selectivity measure will assume a value of $1/N$ if all structures are equally activated by the stimulation rather than the more intuitive 0. To obtain a selectivity of 0 when all structures are equally activated, selectivity can simply be defined as the maximum fraction of activation obtained on the target structure without activation (defined as $f < 0.10$) of any non-target structures [62]. More recently a cost function based approach has also been presented:

$$S_b(I) = RB_b - \frac{\sum_{i=1, i\neq b}^{N} RC_{b,i}}{N-1} \tag{1.2}$$

where selectivity is based on a recruitment benefit RB, e.g. target recruitment $f_b(I)$, and a recruitment cost RC, e.g. the sum of non-target recruitment $f_i(I)$ [60, 61]. The recruitment cost can be limited to ignore non-target activation below a threshold, e.g. 10% activation.

The selectivity is calculated for multiple points on the recruitment curve, i.e. for stimulation currents ranging from bellow recruitment threshold to above full recruitment of the target structure. In order to compress these results to a single selectivity measure, selectivity can be averaged for the full range or part of the recruitment curve or the maximum selectivity can be reported with a minimum current constraint. The motivation for using a minimum recruitment constraint is that high selectivity usually is most difficult to obtain at high levels of activation where the large stimulation currents increase the risk of current spillover. Selectivity obtained at lower stimulation currents can therefore be expected to be at least as high as the maximum selectivity above this constraint. By adopting the constraint of 70% activation from Yoo and colleagues [57], a single measure for the selectivity of an interface can be calculated as

$$\hat{S} = \frac{1}{N}\sum_{i=1}^{N} \max\left\{S_i(I) \mid f_i(I) > 0.7\right\} \tag{1.3}$$

1.3.2 Recording selectivity

Interfaces which are capable of recording single unit activity is a special case where the use of a selectivity index does not make sense, since this already assumes a signal to noise (SNR) level high enough to correctly distinguish and classify action potentials close to the electrodes. Evaluation of such electrodes my instead focus on the number of units that can be monitored and how many types of e.g. sensory stimuli can be distinguished.

For interfaces that are further away from the individual nerve fiber, i.e. outside of the perineurium, the recorded signal is influenced by action potentials from all active fibers within the recording area and is therefore called compound nerve action potentials (CNAP). In some cases intrafascicular recordings may also be evaluated as CNAPs if single units either cannot be identified or an algorithm to do so is not implemented. As for stimulation, the selectivity of such interfaces is typically evaluated on the fascicle level because the fascicles are assumed to constitute functional groups of fibers and at the same time form localized sources in the recording. However, from a practical point of view it does not make sense to use the selectivity definition from stimulation for evaluation of recording performance because the correct detection of an event in the neural activity instead depends on the SNR where non-target activity can be considered noise. If other types of noise are disregarded, selectivity can be expressed in terms of cross-talk where the SNR of a recording channel is the ratio between the potential recorded from the target source and the sum of potentials recorded from non-target sources, i.e. $\frac{V_{target}}{\sum V_{non-targets}}$ [63]. The selectivity ratio (SR) of a device with N channels for recording N sources can then be defined as

$$SR = \left(\prod_{i=1}^{N} \frac{V_{target\ i}}{\sum V_{non-targets}}\right)^{\frac{1}{N}} \tag{1.4}$$

As with stimulation, recruitment curves can be obtained by varying the amount of activity in each fascicle. However, for recording the maximum SNR will be obtained when the target source is maximally activated and the non-target sources are inactive, while a low SNR will be obtained at low levels of activation in the target source and full activation of the non-target sources. Using a constraint of minimum activity would therefore not make sense. Instead, selectivity could e.g. be based on an average over the recruitment curves.

1.4 IMPLANTABLE NERVE INTERFACES

1.4.1 Percutaneous electrodes

Percutaneous electrodes are wire-like interfaces with one or more electrodes (see Figure 1.1), which are inserted through a small incision in the skin, i.e. without open surgery. They are typically used to target nerves in locations where they lie relatively superficial, using anatomical landmarks to estimate the location of the nerve. To ensure optimal placement of the interface a stimulating needle can be used to explore a location where the nerve can be activated with an acceptable stimulation amplitude and without unacceptable adverse effects, i.e. stimulation of non-target neural or muscular tissue. Imaging techniques, in particular ultra sound, can improve implantation by visualizing e.g. soft tissues and providing real time information about the electrode location in relation to the nerve as well as blood vessels and other sensitive tissues during implantation [64-67]. Since percutaneous electrodes are placed outside the nerve, in the best case in immediate proximity of the nerve, and are not shielded from surrounding tissue, e.g. muscles, they are used purely for nerve stimulation. Their low invasiveness does, however, make them suitable for treatment of disorders that would not justify major surgery or for exploratory treatments that lack sufficient evidence for more radical procedures. Percutaneous electrodes are currently in use for pain relief in patients with various types of pain disorders by stimulation of many different peripheral nerves [64-75].

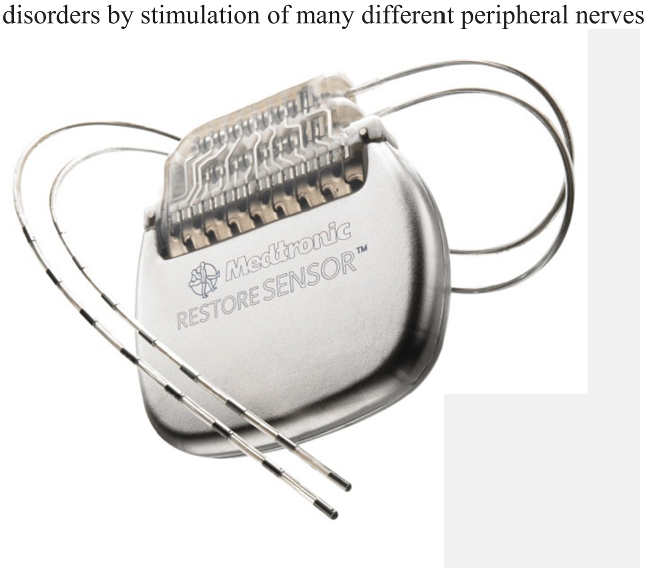

Figure 1.2. Medtronic® Restore Sensor™ for pain relief treatment with two percutaneous leads, each containing eight electrodes (www.medtronic.com).

1.4.2 Epineurial electrodes

Epineurial electrodes are usually ring-shaped electrodes, which are secured to the outside of the target nerve by sewing them to the epineurium, as illustrated in Figure 1.3 [76-80]. The insertion procedure therefore requires open surgery to provide access to the nerve. Like percutaneous electrodes, epineurial electrodes are unsuitable for nerve recording because they do not provide means for shielding the low-amplitude neural signals from noise interference. Compared with percutaneous electrodes, the stimulation selectivity is improved because of the careful placement on the nerve rather than some distance away from it (epineurial recording has been reported, but only of compound action potentials for determining nerve conduction velocity and using an electrode design with a silicone sheet to improve signal quality [81]). Epineurial electrodes may, however, still activate other nerves in the proximity of the target nerve since the interface does not restrict current propagation away from the nerve. The most successful application of epineurial electrodes is for phrenic stimulation where implantation of cuff electrodes is avoided because of the risk of nerve damage caused by pressure to the nerve by the cuff [7]. In this application four electrodes are placed around the circumference of each phrenic nerve (see Figure 1.3). By alternating stimulation between the four electrodes, it is possible to recruit different fiber populations of the nerve and reduce fatigue. This application has been investigated since 1973 and the safety and stability of epineurial electrodes proven in chronic experiments and commercial clinical application [7, 76-78]. Epineurial electrodes have, however, also been considered for other applications, including restoration of locomotion and treatment of fecal incontinence [79, 80].

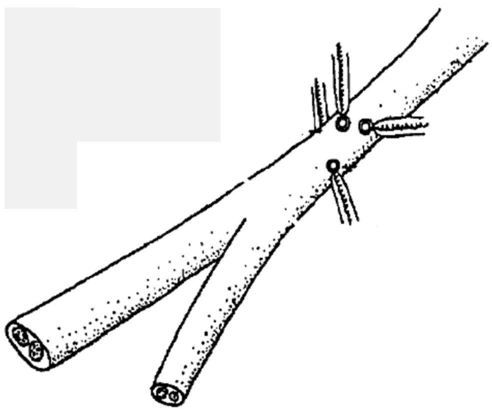

Figure 1.3. Illustration of four epineurial electrodes placed around the circumference of the phrenic nerve. Modified from [76].

1.4.3 Cuff electrodes

Cuff electrodes were among the first to be investigated for use with implanted neural devices and have been extensively applied in both research applications and commercial neural devices for the last four decades [3, 82]. They consist of a cuff made from an insulating material, e.g. silicone [52, 83-89] or polyimide [54, 90-92], with electrodes placed on the inside of the cuff (see Figure 1.4). During implantation the cuff is opened to insert the nerve and then closed to leave the electrodes on the surface of the nerve. Cuff electrodes can be used both for stimulation [52-55, 62, 88, 89, 91, 93-98] and recording [31, 33, 35-37, 40, 43, 44, 63, 82-86, 99-105] and the purpose of the cuff is to contain stimulation currents within the cuff and shield the weak neural signals from noise interference from e.g. nearby muscles to increase the signal to noise ratio.

The electrodes can be arranged in various ways inside the cuff depending on the application. In the most simple versions the electrodes were just bare wires [89, 99], but more commonly rings of e.g. platinum are fixed to the inside of the cuff [83-87, 106], typically in a tripolar configuration with one in the middle and one at each end of the cuff. Although the insulating cuff decrease the amplitude of distant noise sources, such as EMG interference, these currents can still flow through the ends of the cuff and contaminate the nerve signals. It was, however, discovered in early experiments that this tripolar configuration can decrease the noise interference if the two end rings are shorted because this removes the potential gradient necessary for driving the current flow across the length of the cuff [82]. In practice there will be a gradient over the cuff due to electrode impedance, but if the impedances of the electrodes are carefully matched the field will be linear inside the cuff and external sources can be removed by differential filtering [105]. If multiple electrodes are distributed around the inner circumference of the cuff topologically selective stimulation of subareas of the nerve is possible [52-55, 62, 94-98]. The lowest stimulation currents are obtained by stimulating between electrodes spaced longitudinally along the nerve. The stimulation selectivity can, however, be improved by adding one or more anodes to “steer” the stimulation current away from non-target areas of the nerve, e.g., the opposite side of the nerve [55, 107, 108]. Using such techniques, it may be possible to specifically activate a single fascicle of a nerve if it is located in the rim of the nerve. Large multi-fascicular nerves do, however, present a challenge for extra-neural electrodes in activating central fascicles without also recruiting more superficial non-target fascicles. It is possible to overcome this by activating the whole nerve and selectively blocking the non-target area, but this requires high stimulation currents and the selectivity will still be reduced by the larger distance to the electrodes than for superficial fascicles. Topologically selective recording is generally problematic with cuff electrodes [63]. This is because the potential recorded at a given time by one electrode is a weighed sum of all active target and non-target sources within the nerve (plus general noise from distant sources). Even though the amplitude of the potential resulting from an active fiber decreases with the distance between the fiber and electrode a large active non-target fascicle can still produce a significant potential at the electrode hampering selective recording, even for relatively simple nerves [63]. Studies have, however, indicated that velocity selective recording is possible with cuff electrodes if the neural signal is recorded by multiple ring electrodes as it travels along the cuff length. The recordings can then be averaged after adding a delay to each succeeding ring, depending on the expected velocity of the fiber group of interest [102, 109, 110].

Cuff electrodes are the most widely applied type of nerve electrode and has proven that they can safely provide a relatively stable interface for nerve stimulation and recording in chronic studies and commercial use over several decades [89, 99, 100, 111]. Care does, however, need to be taken when implanting them because nerve swelling within the limited space of the cuff can lead to compression and nerve damage after implantation. To avoid this, safe use of cuff electrodes typically requires the inner diameter of the cuff to be 20-40% larger than the nerve diameter, which lowers the performance of the interface by reducing the recorded nerve signals, increasing noise, and reducing selectivity. A special type of cuff electrode, spiral cuffs, was developed specifically to circumvent these problems: Spiral cuff electrodes are designed to curl to a diameter slightly smaller than the nerve diameter, but are capable of adjusting by opening up when the nerve swells and push against the passive spring force of the curled cuff [54, 55, 62, 89, 93, 98, 104].

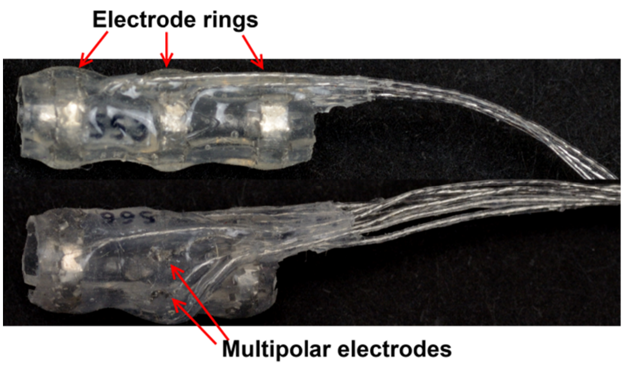

Figure 1.4. Example of a traditional tripolar cuff electrode (top) and a multipolar cuff electrode with multiple electrodes around the nerve for selective stimulation (bottom). Photo by K.R. Harreby.

1.4.4 Special geometry cuff electrodes

The success of cuff electrodes has led to an interest in improving their performance by optimization of either electrode layout and configuration or, less commonly, the geometry of the cuff itself. One example is the multi-groove electrode interface by Koole and colleagues [112], which contain a cuff chamber for each fascicle of the nerve (see Figure 1.5a). Implantation of the interface thus requires splitting the nerve and placing the fascicles individually in the grooves. Excellent stimulation properties with no current spillover to non-target fascicles have been demonstrated in modeling and acute experiments [112]. The electrode is also likely to achieve fascicle selectivity in recording, but such results have not been reported nor have the safety of the interface been demonstrated in chronic studies. Separation of the fascicles could increase the risk of pressure damage as compared to cuff electrodes or would at least increase the size of the implant since each groove will have to contain space for the fascicle to swell after implantation. Multi-groove electrodes would also be impractical for large nerves with significantly more than the four fascicles supported by the design presented by Koole and colleagues.

Cuff electrodes do not necessarily need to be made with a circular cross section, as is usually the case. Some nerves naturally have a more flat shape and cuff electrodes made with an elliptical cross section to better fit such nerves have the advantage of increasing the circumference and thus inter-electrode distance [63]. Tyler and Durand took this concept further by designing the so called flat interface nerve electrode (FINE) to deliberately reshape the nerve into a very flat cross section (see Figure 1.5b) [113]. The FINE cuff is rectangular in shape and made from a silicone elastomer, which apply pressure to the nerve and force the nerve to reshape over a period of a few hours after implantation by redistributing the fascicles and, depending on nerve and FINE geometry, flattening large fascicles [113]. This provides two advantages over circular cuffs, by 1) increasing the circumference enabling more electrodes to be placed, and 2) bringing all fascicles close to the cuff wall thus enabling selective stimulation of fascicles that would otherwise be located in the center of the nerve. This enables the FINE to achieve excellent stimulation selectivity on the fascicle, or even sub-fascicle, level [57, 113-115]. Modeling and acute experiments has also demonstrated that pairs of active fascicles can be distinguished from multipolar FINE recordings if they are sufficiently separated, while fascicles close to each other cannot be distinguished [116]. Recently, methods for increasing the spatial selectivity by using very narrow tripoles have been investigated in modeling studies, but they remain to be experimentally verified and the expected amplitude of the recordings are rather low, indicating high sensitivity to noise [117, 118]. Chronic studies in animals have shown that long-term implantation of FINEs is safe, provided that the geometry of the interface is chosen carefully to avoid compression of the largest fascicles [115, 119]. The FINE has been developed and tested mainly on nerves with relatively few fascicles and it is yet unclear if reshaping of large nerves with many small close-lying fascicles, like the human vagus, median, or ulnar nerves, is safe and practical and if it would maintain fascicle-level selectivity in such an environment. Acute experiments on the large human femoral nerve have, however, indicated that the FINE, although not providing selective activation of all the individual fascicles, is capable of functional and selective activation of at least four of the muscles innervated by this nerve [61].

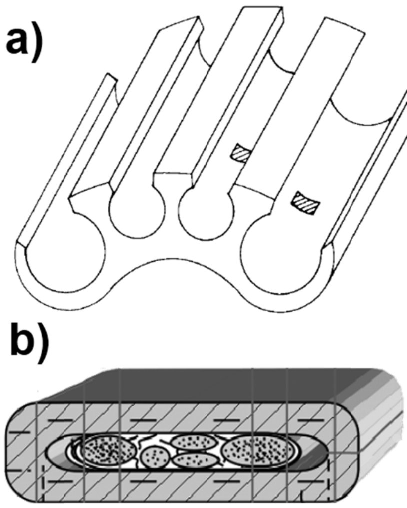

Figure 1.5. Illustration of a) Multi-groove electrode [112], and b) FINE electrode, modified from [113].

1.4.5 Interfascicular electrodes

The interfascicular electrode placement is a rather neglected area in peripheral nerve interfaces; electrodes are nearly always placed either outside the whole nerve, as with epineurial and cuff electrodes, or inside the fascicles. The reason for this is probably that it is regarded as more invasive than extra-neural electrodes, but does not hold promise of immediate gains in selectivity because many fascicles could be relatively close to an interfascicular electrode and spill-over to non-target fascicles therefore would occur soon after reaching the threshold for overcoming the perineurial impedance of the target fascicle resulting in low selectivity as demonstrated by Veltink and colleagues [120]. A method for overcoming these problems was, however, demonstrated by Tyler and Durand: The slowly penetrating interfascicular nerve electrode (SPINE), illustrated in Figure 1.6, is essentially a modified cuff electrode placed around the nerve, but it contains four elements perpendicular to the nerve, which are pushed into the nerve after implantation by the elasticity of the interface, separating the nerve into four champers. The SPINE contains both (interfascicular) electrodes on both sides of the penetrating elements and traditional cuff electrodes on the surface of the nerve and demonstrated both that the interfascicular electrodes provided selectivity that could not be recreated with the cuff electrodes and that electrodes on different sides of the same penetrating element recruited different fascicles [121]. More recently, Tyler and colleagues showed in a modeling study that interfascicular electrodes can obtain excellent selectivity if they are in contact with the target fascicle and only the side facing this fascicles is de-insulated [122]. Interfascicular electrodes in this location provided perfect selectivity of the target fascicle, like intrafascicular electrodes, but had a wider stimulation window than intrafascicular electrodes, making it easier to avoid spill-over to other fascicles, and even with the interfascicular electrode separated from the target fascicle, stimulation selectivity was higher than for extra-neural stimulation [122].

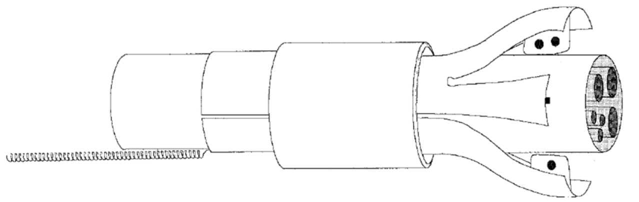

Figure 1.6. Illustration of the slowly penetrating interfascicular nerve electrode, modified from [121].

1.4.6 Intrafascicular electrodes

Intrafascicular electrodes are wire-like interfaces with one or more electrodes, which are inserted inside the fascicles to provide fascicular or sub-fascicular stimulation and recording [56, 58, 59, 123-127, 127-130]. Early versions were made from insulated micro wires. The active electrode sites are made by de-insulating a piece of wire, either at the end of the wire [125, 131, 132], or somewhere in the middle of the wire [125-127, 130]. With the latter method two electrodes can be made on the same wire, if the core is broken in the middle and the wire bent, enabling a controlled distance between the two electrodes. Multiple wire types have been used, but for chronic experiments medical grade wires needs to be used. These typically are typically Teflon coated with a core of Pt-Ir or stainless steel and have a diameter of 25-50 µm. More advanced interfaces have also been developed using metalized polymer fibers, which are more flexible than solid metal wires and can be micro-machined to provide multiple electrodes on a single interface (see Figure 1.7) [56, 128, 129, 133, 134].

The high impedance perineurium acts as a natural cuff around the implanted electrodes containing stimulation current within a single fascicle and reducing noise interference in recordings. Due to the proximity of the electrodes to individual nerve fibers it is possible to record single action potentials. By using algorithms that recognize the shape of recorded action potentials, up to 16 neurons can be monitored by a single electrode. The most crucial factor in determining which neurons are recorded is the fiber to electrode distance; the fibers closest to the electrode are most likely to be recorded, while fiber diameter is less important [130, 135]. It is therefore possible to access a wide range of sensors with a single electrode, but the outcome is determined by which fibers happen to be close to the implanted electrode. Contamination from EMG and other noise sources are a major problem because of the relative small amplitude of the intrafascicular signals, which are in the low µV range. One way of increasing the signal to noise ratio is by using longitudinal intrafascicular interfaces containing multiple electrodes, which are inserted along the fiber direction in a fascicle [130]. Distant sources from outside the fascicle should have a similar effect on all electrodes and can thus be removed by differential recording between the electrodes. However, the interface's alignment with the nerve fibers is crucial; if the interface does not maintain proximity to the same fibers for all electrodes, different fibers will be recorded by each electrode and the differential recording will thus lose selectivity.

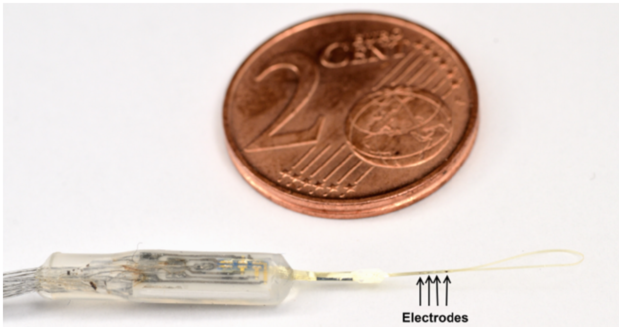

Figure 1.7. Example of a tfLIFE electrode. Only the thin wire-like substrate in the right half of the picture goes into the nerve. Photo by K.R. Harreby.

The longitudinal insertion method is problematic in large multi-fascicular nerves, which may contain 30-40 fascicles, because it requires splitting the nerve and either identifying the particular fascicle(s) of interest or implanting all fascicles of the nerve. This can be extremely cumbersome and produce a bulky implantation (if many fascicles are implanted). An alternative insertion method has therefore been developed in which the intrafascicular interface is inserted transversely to the fiber direction [56]. Pulling a high density interface through the nerve can thus place electrodes in multiple fascicles along a line in the nerve and implanting several interfaces may provide contact to most of the fascicles in the nerve [56, 58]. However, the transverse track through the fascicles deteriorate recording properties since it result in holes in the perineurium close to the electrode, which constitute a current shunt reducing the amplitude of the neural signals and increasing extra-fascicular noise interference in the recordings (unlike longitudinal insertion, where the electrodes can be pulled away from incision holes). It is also challenging to achieve penetration of all the fascicles in large multi-fascicular nerves because the needle will tend to skid off the tough perineurium and take an interfascicular path if it hits the fascicle at an angle.

Intrafascicular electrodes are highly invasive interfaces, which penetrate the natural protecting sheet of the nerve; the perineurium. Lesions may be produced by both the sharp incision procedure and subsequent movement of a rigid interface within the fascicle. Interfascicular electrodes have, however, proven to provide a safe interface in multiple chronic studies, but their recording properties are highly sensitive to build up of connective tissues after implantation since this increase the electrode to fiber distance [125, 127, 129, 131-133, 136]. Controlling the foreign body reaction is therefore extremely important. Polymer-based interfaces are generally advantageous to metal wire interfaces because their higher flexibility enable them to better follow the movements of the nerve and reduce irritation.

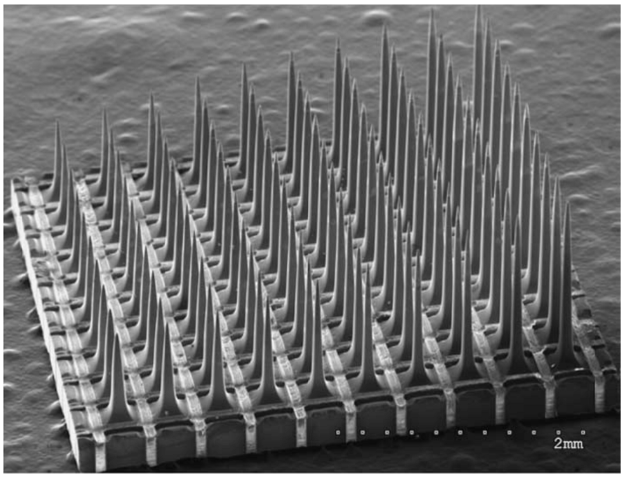

Figure 1.8. The Utah Slanted Array Electrode for peripheral nerves shown here is an adaptation of the Utah Array Electrode previously applied in the cortex. [139]

1.4.7 Penetrating array electrodes

Penetrating array electrodes are also intrafascicular in nature, but their design is fundamentally different from the wire-like structures of the preceding section: originally developed for cortical implantation [137], they consist of multiple, rigid, needle-like structures with a conducting tip which are fixated in an array as shown in the example of Figure 1.8 [138-140]. The array is inserted into the nerve with a high velocity push of a pneumatic device to overcome the resistance of the epineurium and perineurium. Array electrodes can obtain selectivity similar to transverse interfascicular electrodes, i.e. single fiber recordings and fascicle or sub-fascicle stimulation (provided that the electrode ends up inside a fascicle), but have the advantage of placing more electrodes in the nerve: If the needles of the interface have different lengths, as seen in the example of Figure 1.8, electrodes can be placed throughout the whole cross section of the nerve, providing an interface to all the fascicles [138-142]. However, this gain comes at a substantial increase in invasiveness: Although, the electrode location is technically the same, i.e. in the extra-cellular space of the fascicles, the arrays penetrate the nerve with e.g. 100 rigid needles instead of a single flexible wire. To avoid the electrode array being pulled out of the nerve after implantation it is furthermore necessary to fixate it using a cuff around the nerve [139]. Damage to the nerve can be caused by e.g. the pressure exerted to the nerve while pushing the electrode array through, the needle-like electrodes cutting through the fascicles during incision, damage by the electrode tips continued motion in relation to the nerve tissue during movement, and pressure damage if nerve movement is constricted by the rigid array or the cuff around the nerve. Electrode failure during incision can even destroy the nerve completely [138]. Signs of severe nerve trauma after implantation as well as long-term axon degeneration have been reported [139]. Furthermore, a large proportion of the electrodes of the arrays may be lost to e.g. wire breakage and the recording ability of the arrays may disappear altogether after implantation, e.g. due to tissue ingrowth [139]. Recent methodical improvements may, however, enable chronic recording [143].

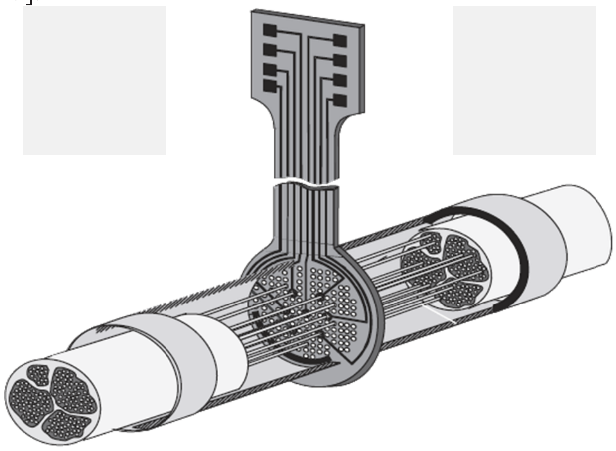

Figure 1.9. Illustration of a polyimide-based regenerative electrode interface with nine stimulation/recording electrodes and one reference electrode. [3]

1.4.8 Regenerative electrodes

Regenerative, or sieve, electrodes are interfaces that are embedded in the nerve by first transecting the nerve and then supporting its regrowth through the interface. The interface typically consists of a tube with a perforated disk (sieve) in the middle, which contains electrodes around some of the holes, as illustrated in Figure 1.9. The ends of the transected nerve are inserted into the tube from each end and the nerve fibers will then be forced to grow through the holes of the sieve to regenerate creating a selective interface to the fibers running through each electrode. In the most extreme case, regenerative electrodes could aim to interface each fiber of the nerve. This is, however, not feasible since current technology is incapable of producing sufficiently small electrodes and growth of multiple fibers through the same hole cannot be avoided. Multiple designs and materials have been employed to manufacture regenerative electrodes, e.g. silicone sieves [144-149], but current designs are based on micro-machined polyimide sieves or micro-channels [150-153]. Nerves have been shown to regenerate through the sieve electrodes and the sieves are useful and selective for both stimulation and recording, although difficulties have been encountered with recording likely due to incomplete regeneration [144-151, 154]. Full nerve regeneration has, however, not been accomplished and long-term implantations suggest that the interface inflict nerve damage on the regenerated nerve fibers [150, 151]. The most likely cause to the majority of this nerve damage is constrictive forces within the holes of the sieve; when the nerve fibers regenerate they will initially be very thin, enabling multiple fibers to connect through the same hole, but as regeneration is completed and the myelin sheath is reestablished they increase in diameter leading to constriction within the holes [150, 151]. Even if all problems currently faced with regenerative electrodes are resolved their use will still be severely limited, since they require transection of the target nerve, which require several months to regrow. In practice this will probably limit them to use in the nerve stubs of amputee limbs for e.g. bi-directional control of prosthetic devices.

1.5 DISCUSSION OF THE PROBLEM AREA

As the interface between the artificial system and the nervous system nerve electrodes is a vital part of a neural prosthetic device that defines the limits of nerve interaction that is possible with the system. Achieving high selectivity in the nerve interface is desirable since it increase the amount of functionality that can be gained; in the ideal case an interface to every single axon in the implanted nerve could e.g. completely restore natural movement after a disabling injury. However, interfaces that are highly selective are usually also very invasive because they rely on reducing the distance between the electrodes and the fibers they interface. The interfaces presented in section III can thus be graded accordingly to their selectivity and invasiveness, as illustrated in Figure 1.10. The least invasive interface that can be considered for neural prosthetic devices is surface electrodes, but as argued previously they also have very low selectivity. In the other end of the scale penetrating array and regenerative electrodes can potentially provide highly selective interfaces to single or small populations of fibers distributed throughout the nerve, but they are also very invasive and involve a high risk of nerve damage. Selecting an appropriate interface for a neural prosthetic device therefore involves assessing the minimum selectivity required to achieve the desired function and determining if the benefit and evidence of the treatment justify the risks of the selected method. Percutaneous electrodes are an interesting option for exploring new treatment modalities or for accessing nerves located in areas where open surgery cannot be performed. Interfaces with intrafascicular electrode locations can provide many functional degrees of freedom, but their invasiveness reduces their application span to e.g. implantation in amputated limps where the risk of nerve damage may be of less concern. Cuff electrodes, however, provide a stable and safe interface for both stimulation and recording, potentially with some selectivity, and have been extensively applied in humans. Methods that improve the selectivity of these already accepted interfaces thus have the potential for displacing their position on the curve of Figure 1.10 to the right, which could improve existing applications and open up new ones.

The feasibility of using cuff electrodes for activating nearly independent groups of fibers within the implanted nerve was first demonstrated by Petrofsky for reducing fatigue and later by McNeal and Bowmann for selective activation of flexors versus extensors [94, 155]. Since then several electrode layouts and stimulation configurations have been investigated with respect to achieving the best possible spatial selectivity in nerve stimulation, e.g., the longitudinal tripolar configuration with or without a transverse steering current. Deurloo and colleagues noted from previous work that spatial selectivity appears to increase when the transverse steering current is increased in the longitudinal configuration and therefore proposed the use of a transverse bipolar or transverse tripolar configuration, previously known from spinal cord stimulation, for improvement of spatial selectivity in peripheral nerve stimulation with cuff electrodes [96, 156, 157]. Modeling results were encouraging indicating that the transverse tripolar configuration can provide higher selectivity than the longitudinal tripolar configuration at the cost of higher stimulation currents [96]. Experiments with 5 or 6 electrode cuffs of 1.5 or 2.0 mm inner diameter placed on the sciatic nerve of rabbits did, however, yield less promising results [53]. These results and modeling of a multi-fascicular nerve [95] led the authors to suggest that the tripolar configuration might be too selective activating only a part of the target fascicle and that the transverse bipolar configuration should be preferred. These results may, however, be caused by the applied electrode design, which leaves very little space between each electrode of the cuff. As indicated by the latter modeling study this may result in a large proportion of the current taking a path through the saline surrounding the nerve and superficial connective tissues of the nerve. The transverse tripolar configuration may therefore still be useful for selective activation of small superficial fascicles if applied with larger electrode spacing. Furthermore, reducing the number of electrodes can simplify the implant e.g. by reducing the number of lead wires. As described previously, cuff electrodes are of interest for both stimulation and recording and the same interface may potentially be used for both in a single application. The requirements for stimulation and recording are, however, conflicting: In order to obtain high field linearization inside the cuff and thus optimize noise reduction to achieve an appropriate signal to noise ratio for recording, the cuff needs to be relatively long [86]. In contrast a relatively short electrode spacing is desired for selective stimulation with longitudinal configurations. The cuff design can then either implement separate sets of electrodes for stimulation and recording or make a trade-off between the two conflicting design criteria. Transverse configurations could thus be an interesting option for obtaining selective stimulation while allowing the cuff dimensions to be based on recording properties and reducing the required number of electrodes.

Another promising approach to improve selectivity is optimization of the electrode design, which aims at producing more selective interfaces without significant increase in invasiveness [112, 113, 121]. A rather overlooked approach to electrode design is to implant electrodes between the fascicles. The lack of interest in this electrode location is probably due to the intuitively low selectivity obtainable with such a location, as demonstrated by Veltink and colleagues [120]. The experimental results of nerve compartmentalization and the recent modeling study of directed interfascicular stimulation does, however, indicate that high levels of selectivity is possible with proper electrode design [112, 121, 122]. Although, interfascicular electrodes are intra-neural they do not compromise the perineurium, which provides crucial protection of the nerve fibers, and may thus be comparable to cuff electrodes in invasiveness depending on their design.

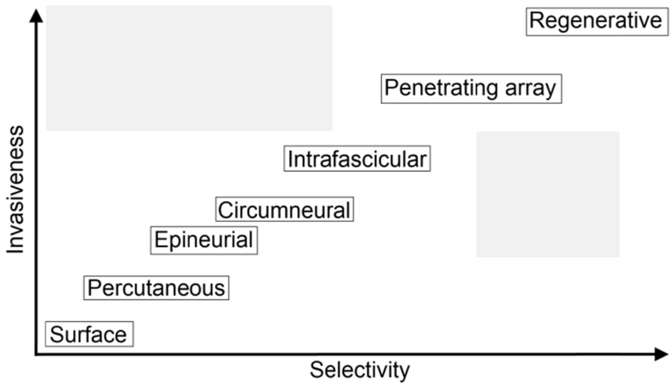

Figure 1.10. Illustration of the relationship between selectivity and invasiveness of the interfaces described in section III.

1.5.1 Contents of the project

In order to investigate the two options singled out above for improving extra-fascicular interfaces to peripheral nerves three studies were conducted. The first study investigated the ability of the transverse tripolar configuration to selectively recruit three nerves of varying size, while the other two introduced a novel interfascicular interface and tested the basic stimulation and recording properties of this interface.

Study 1: Transverse versus longitudinal tripolar configuration for selective stimulation with multipolar cuff electrodes
T. N. Nielsen, G. A. M. Kurstjens and J. J. Struijk
IEEE Trans. Biomed. Eng., vol. 58, pp. 913-919, 2011.

Study 2: Fascicle-Selectivity of an Intraneural Stimulation Electrode in the Rabbit Sciatic Nerve
T. N. Nielsen, C. Sevcencu and J. J. Struijk
Biomedical Engineering, IEEE Transactions on, vol. 59, pp. 192-197, 2012.

Study 3: Comparison of Mono-, Bi-, and Tripolar Configurations for Stimulation and Recording with an Intra-Neural Interface
T. N. Nielsen, C. Sevcencu and J. J. Struijk
To be Submitted.

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Chapter 2.

Transverse vs. Longitudinal Tripolar Configuration for Selective Stimulation with Multipolar Cuff Electrodes

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2.1 ABSTRACT

The ability to stimulate sub-areas of a nerve selectively is highly desirable since it has the potential of simplifying surgery to implanting one cuff on a large nerve instead of many cuffs on smaller nerves or muscles, or alternatively can improve function where surgical access to the smaller nerves is limited. In this study stimulation was performed with a four channel multipolar cuff electrode implanted on the sciatic nerve of nine rabbits to compare the extensively researched longitudinal tripolar configuration with the transverse tripolar configuration, which has received less interest. The performance of these configurations was evaluated in terms of selectivity in recruitment of the three branches of the sciatic nerve. The results showed that the transverse configuration was able to selectively activate the sciatic nerve branches to a functionally relevant level in more cases than the longitudinal configuration (20/27 vs. 11/27 branches) and overall achieved a higher mean selectivity (0.79±0.13 vs. 0.61±0.09, mean±standard deviation). The transverse configuration was most successful at recruiting the small cutaneous and medium sized peroneal branches, and less successful at recruiting the large tibial nerve.

Index Terms—animal experiments, nerve cuff, peripheral nerves, stimulation selectivity

2.2 INTRODUCTION

Neural prosthetic devices utilizing stimulation of peripheral nerves are in use for multiple applications today, including vagal nerve stimulation to treat epilepsy, sacral nerve stimulation to treat urinary and faecal incontinence, phrenic nerve stimulation for ventilator assistance, and peroneal nerve stimulation for correction of foot-drop [1], [2]. A large variety of electrodes have been developed to provide the interface of these systems to the nerve, ranging in invasiveness from percutaneous to extra-neural, intraneural and even regenerative electrodes [2]. The most successful of these interfaces has been the cuff electrode, which has been used for many research and rehabilitation applications for several decades [2]-[4]. Because the cuff electrode has proven to provide a stable and safe interface to the nerve and has been implanted in a large group of patients, research providing optimization of cuff design or stimulation configuration potentially has a large impact in improving existing applications and opening up new ones.

Peripheral nerves typically consist of a number of fascicles, which (at least immediately proximal of nerve bifurcation) have a somatotopic organization, e.g., collecting the nerve fibers innervating one specific muscle. Stimulation configurations that can recruit sub-regions of the nerve with high spatial selectivity may enable a single cuff to control several functions, e.g., antagonist muscles, and thus reduce the need for implantation of cuffs on multiple nerves or muscles.

Petrofsky showed the feasibility of using a cuff electrode with six electrodes placed equidistantly around the sciatic nerve of cats to recruit three nearly independent groups of motor neurons of the gastrocnemius muscle for reduction of fatigue during tetanic contraction by sequential activation of these groups [5]. Later McNeal and Bowmann demonstrated the feasibility of using a seven-electrode cuff on the sciatic nerve of dogs to selectively recruit the ankle flexors vs. extensors using a bipolar configuration (optimally oriented) on each side of the nerve [6]. Since then several cuff designs and stimulation configurations have been investigated with respect to achieving the best possible spatial selectivity in nerve stimulation, e.g., the longitudinal tripolar configuration with or without a transverse steering current. Deurloo and colleagues noted from previous work that spatial selectivity appears to increase when the transverse steering current is increased in the longitudinal configuration and therefore proposed the use of a transverse bipolar or transverse tripolar configuration, previously known from spinal cord stimulation, for improvement of spatial selectivity in peripheral nerve stimulation with cuff electrodes [7]. Modeling results were encouraging indicating that the transverse tripolar configuration can provide higher selectivity than the longitudinal tripolar configuration at the cost of higher stimulation current [7]. Experiments with 5 or 6 electrode cuff of 1.5 or 2.0 mm inner diameter placed on the sciatic nerve of rabbits did, however, yield less promising results [8]. These results and a modeling of a multi-fascicle nerve [9] led the authors to suggest that the tripolar configuration might be too selective activating only a part of the target fascicle and that the transverse bipolar configuration should be preferred.

Research on peripheral nerve electrodes has focused not only on stimulation, but also on recording nerve signals to act as natural sensors, e.g., to determine heel contact in a system to correct foot drop [2], [4], [10]-[13]. In such systems it would be desirable to use the same cuff for both recording and stimulation. In order to obtain high field linearization inside the cuff and thus optimize noise reduction to achieve an appropriate signal to noise ratio for recording, the cuff needs to be relatively long [14]. In contrast a relatively short electrode spacing is desired for stimulation. Since the end electrodes are not used for stimulation with the transverse stimulation configuration, using this configuration for stimulation could allow the cuff length to be optimized for recording. Larger distance between the electrodes of the transverse tripolar configuration should increase the excitation area and might provide more functional nerve recruitment, which could make it an interesting alternative to other configurations.

In this study the performance of the transverse and longitudinal tripolar configurations was compared for a cuff electrode that places four electrodes around the circumference of the nerve, having a longitudinal tripolar length of 15 mm chosen to provide adequate noise rejection for recording.

2.3 METHODS

2.3.1 Surgery

Nine New Zealand White rabbits weighing 3683±222 g (mean±SD) were anaesthetized with subcutaneous injection of 100 mg/kg Ketalar, 5 mg/kg Xylazine and 1 mg/kg Plegicil. Anesthesia was maintained with additional injections of half this dose 20 minutes after the initial injection and then once per hour until the end of the experiment at which point the rabbits were euthanized with an overdose of Pentobarbital. After sedating the rabbit, the skin of the left hind limb was tranquilized with lidocaine and then opened in a line extending from the hip to the knee. The femoral biceps and semitendinous muscles were split from each other to expose the underlying nerves. The sciatic, tibial, peroneal and cutaneous nerves were freed from surrounding tissue from about 3 cm proximal of the branching point to a few cm distal of the branching point. A multipolar cuff electrode (see next section) was then placed around the sciatic nerve, without attempting to align it with the fascicles, and closed with a silicone sheet and a suture at each end and the middle as described by Andreasen et al. [15]. Three ring cuff electrodes were then placed on the tibial, peroneal and cutaneous nerves, respectively, and closed similarly. Finally, the muscles and skin were closed again.

2.3.2 Cuff electrodes

All cuffs were produced accordingly to the technique described by Haugland [16]. The multipolar cuff contained four 0.5x0.5 mm electrodes at 90˚ intervals around the inner circumference at the middle of the cuff and a 1 mm wide ring electrode at each end of the cuff, 7.5 mm from the middle. The cuff had an inner diameter of 2.4 mm, which provided a loose fit around the nerve, and a total length of approximately 17 mm. In addition to this cuff, cuff electrodes were made for recording from each of the three nerve branches. These cuffs had three 1 mm wide ring electrodes with 5 mm between the center of each electrode and a total cuff length of approximately 12 mm. Cuffs with inner diameters of 2.0 or 2.4, 1.6 or 1.8 and 1.0 or 1.2 mm were used for the tibial, peroneal and cutaneous nerves, respectively, to avoid compression of the nerve.

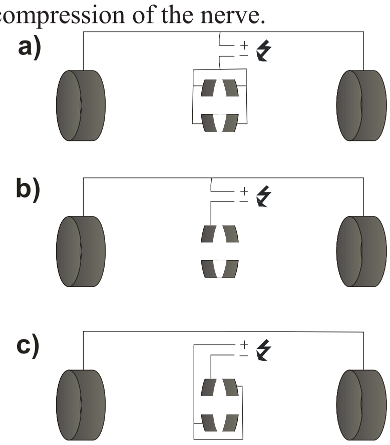

Figure 2.1. Stimulation configurations used in the experiment; a) tripolar ring configuration, b) longitudinal tripolar configuration, and c) transverse tripolar configuration.

2.3.3 Stimulation

Stimulation was applied in tripolar ring, longitudinal tripolar, and transverse tripolar configuration (see Figure 2.1). In the ring configuration the center electrodes were short circuited to constitute a virtual ring and connected to the cathode of the stimulator, while the end electrodes were short circuited and connected to the anode of the stimulator. For the longitudinal configuration each of the center electrodes was connected individually to the cathode while the short circuited end rings were connected to the anode of the stimulator. In the transverse configuration each center electrode was connected in turn to the cathode while the two electrodes immediately at each side of it were short circuited and connected to the anode of the stimulator.

Mono-phasic constant current square pulses of 50 μs pulse width were delivered by a SD9 stimulator with a PSIU6X isolation unit (Grass Technologies). This relatively short pulse width was chosen because of the short distance between stimulation and recording electrodes to ensure separation of the artifact and nerve volley. Recruitment curves were collected for each stimulation configuration by computer controlled stimulation with 10 single pulses at each stimulation intensity for several intensities from below recruitment threshold to above full recruitment of the first recruited nerve branch. The interval between each of the 10 stimulation pulses of the same intensity was randomized between 0.4 and 0.5 s, while each set of pulses were initiated manually. Stimulation intensity was regulated by changing the current while the pulse width was kept constant at 50 μs. Stimulation current was calculated from the linear relationship between the voltage output of the SD9 and the constant current output of the PSIU6X.

2.3.4 Recording

Compound nerve action potentials, recorded by the tripolar ring cuff electrodes on the nerve branches, were preamplified, amplified, filtered, and further amplified using three AI402 SmartProbes and a CyberAmp 380 (Axon Instruments Inc.). The gain was chosen depending on signal amplitude. The signals were high-pass filtered using a first-order filter with -3 dB frequency of 0.1 Hz and low-pass filtered using a fourth-order Bessel filter with a -3 dB frequency of 10 kHz. In animal five and seven it was necessary to increase the corner frequency of the high-pass filter to 1 Hz because high amplitude noise occurred in these animals at low frequencies. The signals were then digitized at 50 kHz using a PCI-6221 ”M series DAQ” with a BNC-2110 connector block (National Instruments) and stored on a computer for further analysis.

2.3.5 Data analysis

Data analysis was performed off-line using Matlab® (The MathWorks^{TM}). A time-average was generated from the responses of each set of 10 stimulus pulses with equal stimulation intensity and the peak-to-peak response (V_{pp}) of the direct nerve volley was calculated from this time average. Each V_{pp} was normalized in each of the nerve branches with respect to the largest V_{pp} obtained during the experiment to express the response as a fraction of full nerve activation (recruitment fraction *f*).
For each stimulation configuration (*c*) and stimulation intensity (*I*) the selectivity index (*S*) was calculated as the response of one nerve branch (*b*) divided by the sum of the responses of all three nerve branches

$$S_{c,b}\left(I\right)=\frac{f_{c,b}\left(I\right)}{\sum_{i=1}^{3}f_{c,i}\left(I\right)} \tag{2.1}$$

in accordance with, e.g., Deurloo and colleagues and Yoo and colleagues [8], [17]. In order to get one number to compare the configurations the selectivity of each configuration was calculated for each animal as the mean of the highest achieved selectivity in recruitment of each nerve branch while activating the branch to at least 70% of its maximum, i.e.,

$$\hat{S}_c=\frac{1}{3}\sum_{i=1}^{3}\max\{S_{c,i}\left(I\right)\mid f_{c,i}\left(I\right)>0.7\} \tag{2.2}$$

If a nerve branch was not activated to more than 70% of maximum by one of the configurations the selectivity of that nerve was set to zero in the calculation of $\hat{S}_c$.

By adaptation of the definition by Yoo and colleagues [17] a nerve branch was regarded as selectively activated in a functionally relevant way by a particular stimulation configuration if both the criteria $S_{c,b}(I) > 0.7$ and $f_{c,b}(I) > 0.7$ were satisfied. For each configuration that fulfilled these requirements the maximally achieved f and the threshold current ($I_{10\%}$) required to produce 10% activation of the nerve branch were found. 10% activation was used instead of 0% to make the threshold more clearly defined and was found by linear interpolation of the two closest points on the recruitment curve in accordance with, e.g., Deurloo et al. [8].

The results were compared using the Mann-Whitney U Test for statistical analysis.

2.4 RESULTS

Table 2.1. The number of animals (of nine) in which the various nerves could be selectively activated for the three configurations.

	Tibial	Peroneal	Cutaneous
Tripolar ring	0	3	0
Longitudinal tripole	0	8	3
Transverse tripole	2	9	9

Table 2.2. Selectivity index of each electrode configuration overall and for each nerve branch separately.

	Ring (mean±SD)	Longitudinal (mean±SD)	Transverse (mean±SD)
$\hat{S}_c$	0.40±0.08	0.61±0.09	0.79±0.13
S_c (tibial)	0.40±0.05	0.44±0.09	0.43±0.37
S_c (peroneal)	0.47±0.26	0.80±0.14	0.98±0.01
S_c (cutaneous)	0.33±0.15	0.57±0.16	0.95±0.08

In the nine animals 3/27(11%) nerve branches were selectively activated in a functionally relevant way by the tripolar ring configuration (tibial nerve zero times, peroneal nerve three times, and cutaneous nerve zero times), 11/27(41%) nerve branches were selectively activated in a functionally relevant way by the longitudinal tripolar configuration (tibial nerve zero times, peroneal nerve eight times, and cutaneous nerve three times), while this was 20/27(74%) for the transverse tripolar configuration (tibial nerve two times, peroneal and cutaneous nerves nine times each), see Table 2.1.

The tripolar ring configuration achieved a selectivity index of 0.40±0.08 (mean±SD), the longitudinal configuration achieved a selectivity index of 0.61±0.09, and the transverse configuration achieved a selectivity index of 0.79±0.13. The selectivity ($\hat{S}_c$) of the ring configuration was significantly lower (p=0.000) than for the longitudinal configuration, which was significantly lower than for the transverse configuration (p=0.005). As can be seen in Table 2.2 the selectivity of the transverse configuration was reduced by a low selectivity in recruiting the tibial nerve. The selectivity in recruitment of the tibial nerve was this low because the transverse configuration failed to achieve an activation of the tibial nerve of $f > 0.7$ in three animals and the selectivity in these animals therefore was set to zero (animal 3, 4, and 8). There is no significant difference between the longitudinal and transverse configurations in selectivity of the tibial nerve, while the difference is significant for the peroneal and cutaneous nerves ($p = 0.894$, $p = 0.000$, and $p = 0.000$, respectively). The selectivity of the ring configuration is not significantly different from either the longitudinal or transverse configurations for the tibial nerve ($p=0.122$ and $p=0.626$, respectively), while it is significantly different for both the peroneal nerve ($p=0.002$ and $p=0.000$, respectively) and cutaneous nerve ($p=0.007$ and $p=0.000$, respectively).

For the nerve branches that were selectively activated, the ring configuration achieved a maximum selective activation of $max(f) = 0.89 \pm 0.10$, the longitudinal configuration achieved a maximum selective activation of $max(f) = 0.87 \pm 0.09$, and the transverse configuration achieved a maximum selective activation of $max(f) = 0.90 \pm 0.09$. The stimulation current required to achieve activation to 10% of maximum in the target branch was 145±96 μA for the ring configuration, 111±46 μA for the longitudinal configuration and 453±295 μA for the transverse configuration. The difference in $max(f)$ was not significant for the longitudinal and transverse configurations while $I_{10\%}$ was significantly lower for the longitudinal configuration ($p = 0.265$ and $p = 0.001$, respectively). Neither $max(f)$ nor $I_{10\%}$ of the ring configuration is significantly different from either the longitudinal ($p=0.484$ and $p=0.697$, respectively) or transverse configuration ($p=0.927$ and $p=0.083$, respectively).

Figure 2.2 shows a typical example of recruitment data; this was recorded from animal 8. The figures in each row use the same center electrode as cathode, but the left column of figures uses the short circuited end electrodes as anodes, while the right column uses the short circuited center electrode at either side of the cathode as anodes. Not surprisingly the same cathode seem to recruit the same nerve branch regardless of the configuration, but for channel one and two, the transverse anodes have the effect of suppressing the recruitment of the non-target nerve branches increasing the selectivity in recruitment of the peroneal and cutaneous nerves. It should be noted that the longitudinal configuration did fulfill the requirements for functionally selective activation of the peroneal nerve, but the transverse configuration still improved the recruitment characteristics to achieve $f = 0.99$ with a selectivity of 0.98. It can also be observed that especially the tibial nerve did not conform to a sigmoidal recruitment curve, but was instead recruited to a plateau of $f \approx 0.2$ (at which point a clear twitch response could be observed visually) before achieving the full recruitment at a much higher stimulation amplitude. For the transverse configuration this final increase required such high amplitude that full activation of the tibial nerve was not achieved.

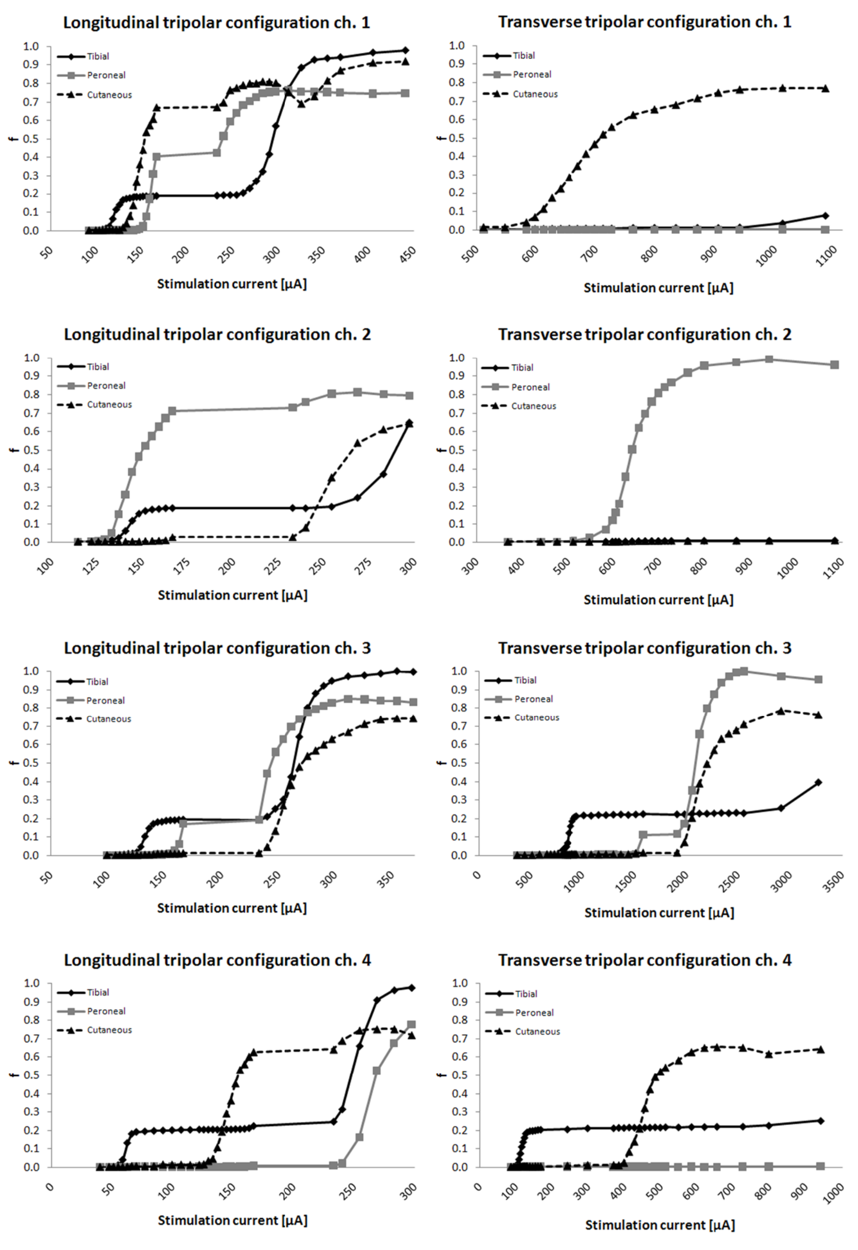

Figure 2.2. Recruitment curves of the three nerve branches for the longitudinal and transverse tripolar configurations, respectively, for animal 8. The channels of each configuration are comparable in the way that the electrode used for cathode in longitudinal ch. 1 is the same as used for cathode in transverse ch. 1 and so forth.

2.5 DISCUSSION

This study has presented the experimental results of stimulating with two multipolar configurations, the longitudinal and transverse tripolar configuration, respectively, and compared these results with the tripolar ring configuration. The transverse tripolar configuration outperformed the longitudinal configuration, both in terms of number of functionally relevant selectively activated nerve branches and selectivity, whereas the longitudinal configuration outperformed the ring configuration. Despite theoretically providing uniform non-selective stimulation the ring configuration managed to fulfill the criteria for functionally relevant selective activation in three cases for the peroneal nerve. This result could be caused by particularities in nerve geometry, unbalanced impedance of the four center electrodes, and positioning of the nerve inside the cuff. Overall the peroneal nerve was the most often, functionally relevant and selectively activated nerve branch, whereas the tibial nerve was the most difficult to activate selectively. This could be because full activation of the tibial nerve requires stimulation of a large proportion of the sciatic nerve without stimulation of the other fascicles.

As expected the increased spatial selectivity of the transverse configuration as compared to the longitudinal configuration comes at the cost of an increase in stimulation current. The threshold current varied widely between animals and nerves, especially for the transverse configuration, but on average the transverse configuration required 4.1 times higher current to reach $I_{10\%}$ than the longitudinal configuration. In previous studies Deurloo and colleagues found the ratio between threshold current of the transverse tripolar configuration and the monopolar configuration to be 5.4 from a modeling study [9] and 10.6 from experimental work [8]. Considering the high variability in $I_{10\%}$ the results of the current experiment seem to be in reasonably agreement with literature. Differences could be caused by, e.g., lower threshold current of the monopolar than the longitudinal configurations [18], the shorter electrode spacing used by Deurloo and colleagues and increased thickness of the saline layer in our study. The high variability in threshold current for the transverse configuration may be expected because the excitation area is narrower than for the longitudinal configuration, thus yielding a higher sensitivity to the exact nerve-electrode geometry.

In the previous experimental work on the transverse tripolar cuff configuration for stimulation of peripheral nerves Deurloo and colleagues reported selectivity in terms of the ability to selectively recruit each of the four muscles lateral gastrocnemius (LG), soleus, tibialis anterior, and extensor digitorum longus (EDL) [8]. Because the tested configurations failed to activate agonist muscles independently of each other the analysis focused on selectivity in recruitment of the antagonist muscles LG vs. EDL equivalent to recruiting part of the tibial nerve vs. part of the peroneal nerve. In contrast in the present study selectivity was measured as the ability to recruit each of the three nerve branches emanating from the sciatic nerve just distal of the cuff position. Since the sciatic nerve fibers at this point presumably are organized branch-wise this provides an opportunity to investigate the spatial extent of stimulation in the sciatic nerve and compare recruitment of a small (cutaneous), medium (peroneal), and large (tibial) nerve whereas the organization of the motor neurons of different muscles at the level of the sciatic nerve is more uncertain. Another difference between the two studies is the applied cuff design: Deurloo and colleagues used a tight-fitting 1.5 mm diameter cuff with five electrodes (four animals) or 2.0 mm cuff with six electrodes (one animal) [8] while a loose-fitting 2.4 mm cuff with four electrodes was used in the current study. The results presented here demonstrate that even with the thicker saline layer the transverse tripolar configuration is capable of achieving excellent selectivity in recruitment of small and medium sized fascicles. From the results of both experimental studies and the knowledge gained from the modeling studies [7], [9] the angular distance between electrodes appears to be of vital importance to the extent of the activation area and thus to the performance of the transverse configuration and should be chosen accordingly to the size of the target fascicles.

The exact angular location of the central electrodes with respect to the fascicles will influence the cuff electrode's ability to provide selective stimulation. Ideally, an electrode should be placed over the middle of each fascicle, and in the case of the transverse configuration the anode electrodes should be placed at either side of each fascicle. The easiest way to produce cuffs is, however, with equal angular electrode spacing, and more importantly anatomical variance makes custom made cuff designs impractical. Furthermore, orienting the cuff during implantation can be difficult because the fascicles are not always clearly distinguishable and it might be impossible to orient it perfectly for all fascicles of the nerve at the same time. In chronic applications maintaining the orientation from the time of implantation until encapsulation by connective tissue has taken place is a challenge. The transverse tripolar configuration should be expected to be more sensitive to orientation of the cuff because of the more narrow area of excitation. The results did, however, show that it was able to selectively stimulate the peroneal and cutaneous branches in all nine animals despite of this. Our experiment did not include an evaluation of nerve-electrode anatomy, but given the nine cases of blind implantation there presumably were both animals with rather good and rather bad cuff orientation.

Deurloo and colleagues discouraged the use of the transverse tripolar configuration as it was reported to generally provide too narrow an area of activation for selective stimulation of a whole fascicle [9]. The usefulness of the transverse tripolar configuration does, however, not only depend on the number of branches that can be selectively activated to an acceptable level of activation, but also improvement in the recruitment characteristics obtained in individual cases is important. A practical approach to achieve maximal functionality in practical applications is to use a number of different configurations and find the one that provides the best performance for each desired functionality in each patient, as demonstrated experimentally by Tarler and Mortimer [19]. The potential value of the transverse configuration is illustrated in Figure 2.2 where the anodes of the transverse configuration have the effect of suppressing the non-target nerve branches to substantially improve the performance in recruitment of the peroneal and cutaneous nerves. The performance of the transverse tripolar configuration depends on, e.g., the electrode spacing, which determine how large a proportion of the nerve is activated, and the size and position of the target fascicle. Including the transverse tripolar configuration in a stimulation paradigm could therefore improve selective stimulation of smaller fascicles, while other configurations could be used for stimulating larger fascicles, e.g., monopolar, transverse bipolar, or double cathodal configurations. Alternatively the transverse tripolar configuration could be modified to a quadrupolar configuration with the two center electrodes as a short circuited cathode, i.e., a virtual “wide” transverse tripolar configuration (see Figure 2.3), or asymmetrical transverse tripolar stimulation could be applied to steer the field [20].

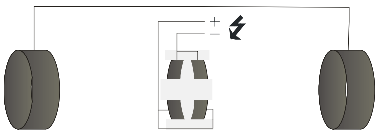

Figure 2.3. Illustration of a transverse quadrupolar, or virtual “wide” tripolar, configuration.

In both our study and the previous studies by Deurloo and colleagues the transverse tripolar configuration has been investigated exclusively with respect to stimulation properties, while the configuration’s recording properties still remain to be investigated. It is possible that the relatively short distance between the electrodes in the transverse configuration will provide high spatial selectivity. The short distance would, however, probably also result in low amplitude of the nerve recordings. Furthermore, with the transverse location of the electrodes recordings would probably be more susceptible to contamination by noise sources lying outside the cuff, such as electromyographic signals. The transverse stimulation configuration could, however, possibly be combined with a longitudinal recording configuration. This would allow cuff design to focus on optimizing recording performance, while only the choice of center electrodes would determine stimulation properties.

2.6 CONCLUSIONS

The spatial selectivity of the transverse tripolar configuration was investigated and compared to the longitudinal tripolar configuration in the sciatic nerve of nine animals. The transverse configuration outperformed the longitudinal configuration in terms of number of branches that was selectively activated and overall selectivity. In particular, the transverse configuration was able to selectively recruit the small cutaneous and medium sized peroneal nerve braches. The transverse tripolar configuration is probably not a good choice for activating large or deep-lying fascicles, but in combination with other configurations it could provide an interesting option for peripheral nerve stimulation.

ACKNOWLEDGMENT

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Chapter 3.

Fascicle-Selectivity of an Intra-Neural Stimulation Electrode in the Rabbit Sciatic Nerve

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3.1 ABSTRACT

Current literature contains extensive research on peripheral nerve interfaces, including both extra-neural and intrafascicular electrodes. Interfascicular electrodes, which are in-between these two with respect to nerve fiber proximity have, however, received little interest. In this proof-of-of concept study an interfascicular electrode was designed to be implanted in the sciatic nerve and activate the tibial and peroneal nerves selectively of each other, and it was tested in acute experiments on nine anaesthetized rabbits. The electrode was inserted without difficulty between the fascicles using blunt glass tools, which could easily penetrate the epineurium but not the perineurium. Selective activation of all tibial and peroneal nerves in the nine animals was achieved with high selectivity ($\hat{S}$ = 0.98±0.02). Interfascicular electrodes could provide an interesting addition to the bulk of peripheral nerve interfaces available for neural prosthetic devices. Since interfascicular electrodes can be inserted without fully freeing the nerve and have the advantage of not confining the nerve to a limited space, they could, e.g., be an alternative to extra-neural electrodes in locations where such surgery is complicated by blood vessels or fatty tissue. Further studies are, however, necessary to develop biocompatible electrodes and test their stability and safety in chronic experiments.

Index Terms—animal experiments, interfascicular electrode, nerve stimulation, peripheral nerves, stimulation selectivity.

3.2 INTRODUCTION

Neural prosthetic devices utilizing stimulation of peripheral nerves are in use for multiple applications, including vagus nerve stimulation to treat epilepsy, sacral nerve stimulation to treat urinary and faecal incontinence, phrenic nerve stimulation for ventilator assistance, and peroneal nerve stimulation for correction of foot-drop [1]-[8]. A large variety of electrodes have been developed to provide the interface of these systems to the nerve, ranging in invasiveness from percutaneous to extra-neural, intraneural and even regenerative electrodes [8].

The most used electrode for peripheral nerve stimulation has been the extra-neural cuff electrode, which has been used for many research and rehabilitation applications for several decades [9]-[18], but also intrafascicular electrodes have received considerable interest over the last two decades [19]-[26]. The interfascicular electrode, being the intermediate stage between the cuff electrode and the intrafascicular electrode with regard to electrode placement, has received less interest.

Peripheral nerves typically consist of a number of fascicles, which (at least immediately proximal to a nerve bifurcation) have a somatotopic organization, in which the nerve fibers are grouped according to the nerve branch to which they belong. Stimulation electrodes that can recruit sub-regions of the nerve with a high spatial selectivity may therefore enable a single interface to control several functions, e.g., antagonist muscles, and thus reduce the need for implantation of electrodes on multiple nerves or muscles.

In a modeling study Veltink and colleagues found that a single electrode contact placed in the epineurium just outside a fascicle cannot selectively activate fascicles [27]. This is a rather intuitive result since several fascicles were within a relative short distance of the electrode and the impedance of the perineurium must be overcome before the fascicle can be activated. However, Tyler and Durand did achieve excellent topological selectivity with the so-called slowly penetrating interfascicular nerve electrode (SPINE) [28]. This result was achieved by using passive elements to electrically shield different topological areas of the nerve from each other. Careful electrode design that includes such elements to shield non-target fascicles from the stimulating contact could thus be a solution for bypassing the problems demonstrated by Veltink and colleagues to achieve high selectivity with an interfascicular electrode.

From a surgical point of view implanting cuff electrodes can be cumbersome in some locations due to the requirement to free the nerve of surrounding tissue such as blood vessels, whereas implantation of intrafascicular electrodes is a relatively invasive and laborious procedure, requiring penetration of the perineurium and with a sharp needle. An electrode designed to be pushed through the relative soft epineurium without lifting and freeing the nerve could provide a relatively less invasive means of placing electrode contacts in close proximity of the nerve fibers. This should yield a current consumption low enough for an implanted system and a selectivity at least to the level of sub-nerve activation.

In the current study a four-contact interfascicular electrode was developed and its selectivity for stimulation was tested in the sciatic nerve of nine rabbits. The electrode was designed to facilitate a blunt insertion into the nerve without penetrating the perineurium or lifting the nerve and to contain a passive element separating the contact set on one side of the electrode from the contact set on the other side. The hypothesis of this study was that such an electrode configuration would enable selective stimulation of two different topological areas of the nerve whilst simplifying the implant procedures.

A preliminary version of this work has been reported [29].

3.3 METHODS

3.3.1 Electrodes

The interfascicular electrode developed for the experiment is illustrated in Figure 3.1. It consisted of an 8 mm long piece of flattened nylon tube (0.63 mm outer diameter) with a nylon suture used for pulling the electrode into the nerve, and four circular Ag contacts of approximately 0.5 mm diameter. Silver was used for the contacts because it is relatively easy to manipulate. The contacts were placed in longitudinal pairs on each side of the flattened tube with 2 mm between the middle of each contact of the pair. The total width of the electrode was less than 1 mm.

To fabricate the interfascicular electrode an 8 mm piece of 0.50/0.63 mm (inner/outer) diameter nylon tube (Portex® 800/200/100/100) was flattened and four pieces of 75/140 µm (without/including insulation) Teflon® insulated silver wires (A-M Systems, Inc.® no. 785500) were cut. The tube was elongated 2 mm from one end and a nylon suture with a knot at the end was inserted through the other end of the tube (see Figure 3.2a). One end of each wire was melted into an approximately 0.5 mm diameter bulb. On each side of the flattened tube holes were made with a needle at a distance of 2 and 4 mm from the non-elongated end. The silver wires were then inserted through these holes and the bulbs were glued to the outside of the tube with drops of super glue (Figure 3.2b and c). The tube was filled with silicone and the bulbs were grounded down until they only emanated slightly from the wall of the tube (Figure 3.2d). Finally, the silver wires were coiled for strain-relieve and soldered onto the four leads of a shielded lead cable.

The impedance between the two contacts of each channel of the interfascicular electrode was measured in saline before and after the experiment. In addition, the impedance was measured after euthanizing each rabbit. Both types of measurements were performed at 1000 Hz using a component tester (Megger® LCR131-EN).

Cuff electrodes for recording from the tibial and peroneal nerves were produced according to the technique described by Haugland [30]. The cuffs were 12 mm long and contained three 1 mm wide Pt ring contacts placed with 5 mm between the middle of each ring.

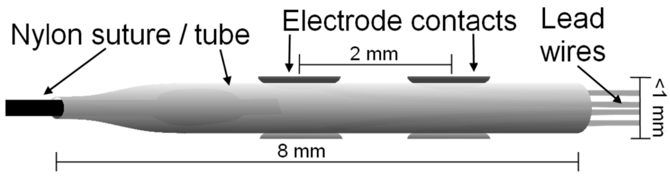

Figure 3.1. Illustration of interfascicular electrode with four Ag contacts. Not drawn to scale. [29]

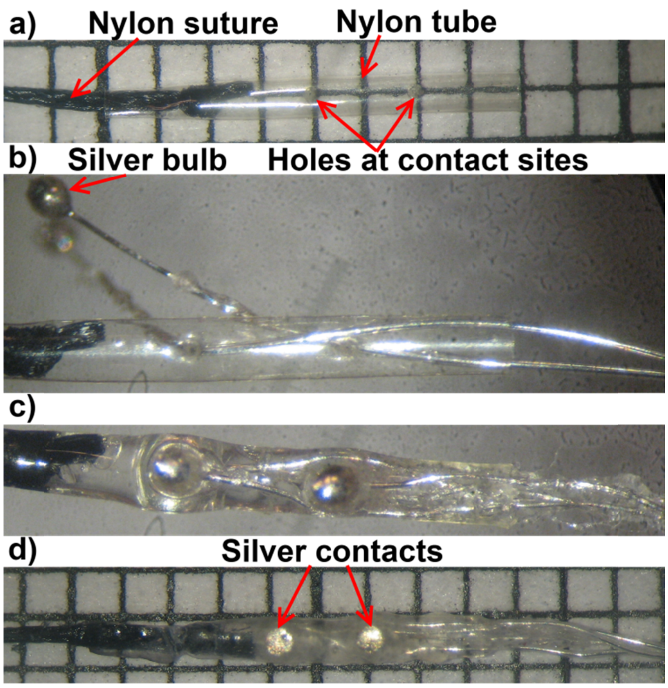

Figure 3.2. Fabrication of interfascicular electrodes: a) A piece of Nylon tube is cut, flattened, and elongated at one end. A nylon suture with a knot is pulled into the tube and two holes are made on each side of the tube. b) Silver wires with bulbs on the ends are pulled through the holes in the tube. c) The bulbs are secured in place with super glue and the tube is filled with silicone. d) The bulbs are grinded down to leave flat contacts. The grid shown behind the electrode in a) and d) has 1 mm between the lines.

3.3.2 Surgery

Nine rabbits weighing 3894±216 g (mean±SD) were anaesthetized with subcutaneous injection of 100 mg/kg Ketalar, 5 mg/kg Xylazine and 1 mg/kg Plegicil. Anesthesia was maintained with additional injections of half this dose 20 minutes after the initial injection and then once per hour until the end of the experiment, at which point the rabbits were euthanized with an overdose of Pentobarbital. After inducing the anesthesia, the skin of the left hind limb was tranquilized with lidocaine and then opened in a line extending from the hip to the knee of the left hind leg. The femoral biceps and semitendinous muscles were split from each other to expose the underlying nerves. The interfascicular electrode was implanted in the sciatic nerve distal to the muscular branch with one pair of contacts facing the tibial fascicle and the other pair facing the peroneal fascicle. This insertion was made by piercing the epineurium with a blunt glass needle of 1 mm diameter, pushing the needle along the direction of the nerve for about 2 cm in-between the fascicles, and then piercing the epineurium at the other end of this canal (see Figure 3.3a). A glass noose was then inserted in the canal created by the needle, the suture of the electrode (see following section) was attached to the noose (see Figure 3.3b), and the electrode was then pulled into the nerve by retracting the glass noose (see Figure 3.3c). The tibial and peroneal nerves were freed for a few cm distal to the bifurcation of the sciatic nerve and a cuff electrode was placed around each nerve for recording. The distance between the interfascicular electrode and the cuff electrodes was about four cm.

3.3.3 Stimulation

Mono-phasic constant current square pulses of 50 µs were delivered by a SD9 stimulator with a PSIU6X isolation unit (Grass Technologies). This relatively short pulse width was chosen because of the short distance between stimulation and recording electrodes to ensure separation of the artifact and nerve volley. Recruitment curves were obtained by computer triggered stimulation with 10 single pulses at each stimulation intensity for several intensities, ranging from below recruitment threshold to above full recruitment of the first recruited nerve branch. The interval between each of the 10 stimulation pulses of the same intensity was randomized between 0.4 and 0.5 s, while each set of pulses was initiated manually. Stimulation intensity was regulated by changing the current while the pulse width was kept constant at 50 µs. Stimulation current was calculated from the linear relationship between the voltage output of the SD9 and the constant current output of the PSIU6X. Stimulation with the interfascicular electrode was bipolar using the distal contact of each side as cathode and the proximal contact of the same side as anode.

3.3.4 Recording

Recorded nerve signals were preamplified, amplified, filtered, and further amplified using two AI402 SmartProbes and a CyberAmp 380 (Axon Instruments Inc.). The gain was chosen depending on signal amplitude. The signals were high-pass filtered using a first-order filter with -3 dB frequency of 0.1 Hz and low-pass filtered using a fourth-order Bessel filter with a -3 dB frequency of 10 kHz. In animal two and five it was necessary to increase the corner frequency of the high-pass filter to 1 Hz because of the presence of high intensity noise at low frequencies. The signals were then digitized at 16 bits resolution and 50 kHz using a PCI-6221 ”M series DAQ” with a BNC-2110 connector block (National Instruments) and stored on a computer for further analysis.

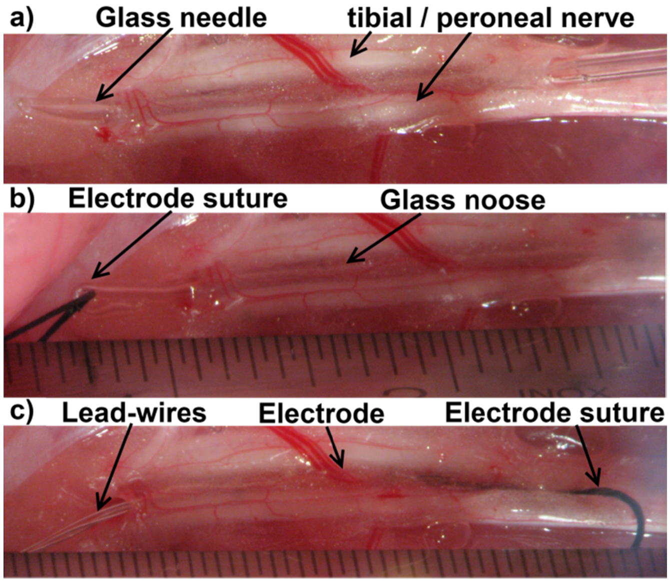

Figure 3.3. Step-by-step pictures of the insertion of the interfascicular electrode in a rabbit sciatic nerve; a) glass needle inserted in sciatic nerve, b) glass noose inserted, c) interfascicular electrode inserted. The left side of the images is proximal, the right side is distal. In each image the tibial fascicle is at the top and the peroneal fascicle at the bottom. The ruler at the bottom has one line for each 0.5 mm.

3.3.5 Data analysis

Data analysis was performed off-line using Matlab® (The MathWorks™). A time-average was generated for each set of 10 stimuli with equal stimulation intensity and the peak-to-peak response (V_{pp}) of the direct nerve volley was calculated from this time average. Each V_{pp} was normalized in each of the nerve branches with respect to the largest V_{pp} obtained during the experiment to express the response as a fraction (f) of full nerve activation.

For each stimulation intensity (I) the selectivity index (S) was calculated as the response of the target nerve branch (b) divided by the sum of the responses of both nerve branches:

$$S_b(I) = \frac{f_b(I)}{f_{tibial}(I) + f_{peroneal}(I)} \tag{3.1}$$

in accordance with, e.g., [31], [32]. To get a single number to measure the selectivity of the electrode, it was calculated as the mean of the highest achieved selectivity in recruitment of each nerve branch while activating the branch to at least 70% of its maximum, i.e.:

$$\hat{S} = \frac{1}{2}\sum_{i=1}^{2}\max\left\{S_i\left(I\right) \mid f_i\left(I\right) \geq 0.7\right\} \tag{3.2}$$

Adapting the definition provided by Yoo et al [32], a nerve branch was regarded as selectively activated in a functionally relevant way if both the criteria $S_b(I)>0.7$ and $f_b(I)>0.7$ were satisfied.

In addition, the maximally achieved f and the threshold current ($I_{10\%}$), required to produce 10% activation of the nerve branch were obtained.

The results were compared using the Mann-Whitney U Test for statistical analysis.

Table 3.1. Results of stimulating with the interfascicular electrode summarized for each nerve and for both nerves combined.

	Interfascicular electrode		
	Tibial	**Peroneal**	**Overall**
S	0.97±0.04	1.00±0.00	0.98±0.03
f	1.00±0.01	0.96±0.05	0.98±0.04
$I_{10\%}$	542±201	287±104	415±210

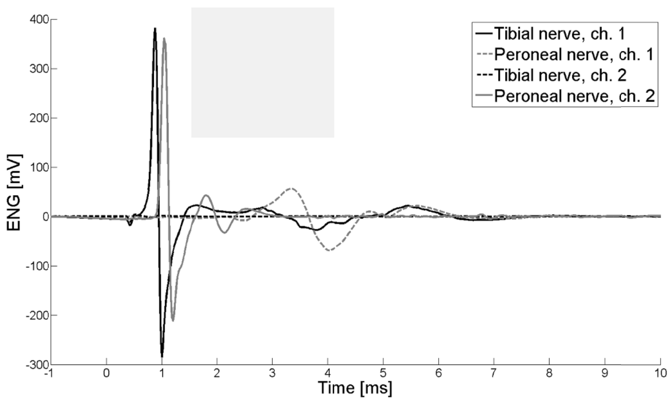

Figure 3.4. CNAPs recorded from the tibial and peroneal nerves as responses to stimulating with channels 1 and 2 of the interfascicular electrode, respectively, in animal 1. In both cases the applied stimulation current was 654.6 µA, which fully activated the target nerve (see Figure 3.5).

3.4 RESULTS

The interfascicular electrode achieved functional selective stimulation of all 18 tibial and peroneal nerve branches tested in the experiment with $\hat{S}$ = 0.98±0.02 (mean±SD) and with f up to 0.98±0.04 (see Table 3.1). The selectivity was slightly higher for the peroneal nerve than for the tibial nerve ($S_{peroneal}$ = 1.00±0.00 vs. S_{tibial} = 0.97±0.04, p=0.009) whereas the maximal selective response did not differ significantly (f_{tibial} = 1.00±0.01, $f_{peroneal}$ = 0.96±0.05, p=0.292). The threshold current for stimulating the nerves was $I_{10\%}$ = 415±210µA (0.02µC per stimulus pulse) with the peroneal nerve requiring significantly lower current than the tibial nerve (287±111µA vs. 542±213µA, p=0.003).

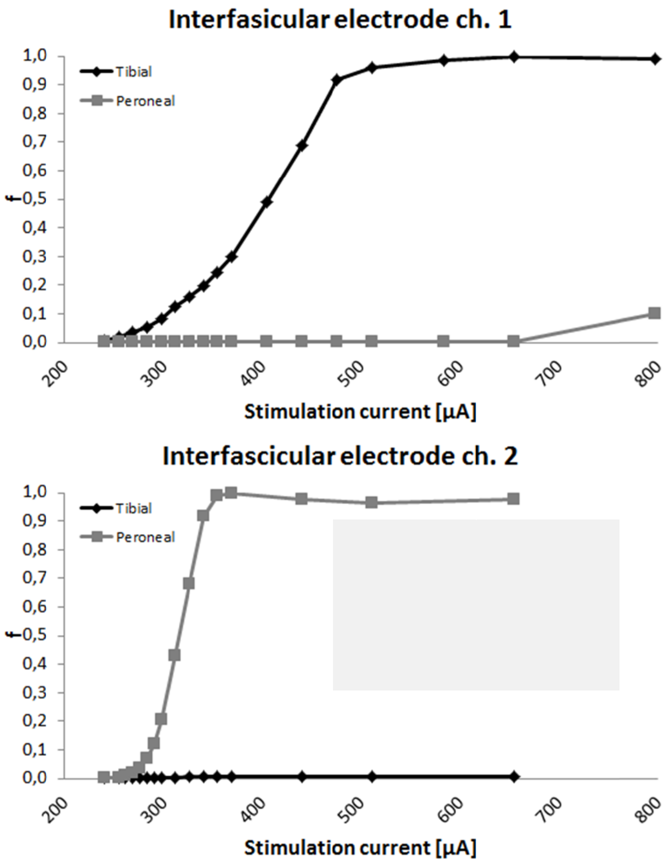

Figure 3.5. Recruitment curves obtained from animal 1 with the interfascicular electrode.

Figure 3.4 shows an example of the CNAPs recorded during the experiment. The figure summarizes the time averages from stimulation with channel 1 and 2, respectively, of the interfascicular electrode in animal 1. In both cases a stimulation amplitude of 654.6 µA was applied, which fully activated the nerve (see Figure 3.5). It can be observed that the response occurred slightly later in the peroneal nerve than in the tibial nerve, which was a general tendency across the animals. To calculate the V_{pp} a time window was identified for the response of each nerve in each animal. In this animal this window was [0.75, 1.5] ms for the tibial nerve and [0.8, 1.8] ms for the peroneal nerve, respectively.

The results from animal 1 are presented in Figure 3.5 as an example of stimulation with the interfascicular electrode. In this experiment both nerves were fully activated, i.e., max(f_{tibial}) = max($f_{peroneal}$) = 1 with a selectivity of $\hat{S}$ = 0.99 (S_{tibial} = 1.00, $S_{peroneal}$ = 0.99) and stimulation current of $\hat{I}_{10\%}$ = 287μA.

The impedances measured after euthanizing the animals are presented in Table 3.2. The impedances were highest for the peroneal nerve of animal seven, after this animal one of the lead wires broke. On average the impedance was higher for the peroneal than for the tibial channel, but this difference was not statistically significant (14.4 vs. 11.4 kΩ, $p = 0.171$).

Table 3.3 lists the impedance of the electrodes measured right after fabrication of the electrodes and again after using the electrodes in five (no. 1) and two (no. 2) animals of the experiment, respectively.

Table 3.2. In vivo impedance measured between the two contacts of each stimulation channel of the interfascicular electrode after the end of each experiment. The electrode used for the initial experiments was damaged (a broken lead wire) after animal 7 and electrode no. 2 was therefore used for the last two animals.

Animal	Electrode no.	Impedance [kΩ]	
		Tibial	Peroneal
1	1	17.3	17.5
2	1	8.0	12.2
3	1	8.9	9.3
4	1	16.0	15.9
5	1	10.0	14.5
6	1	13.9	13.0
7	1	13.7	24.9
8	2	6.8	12.4
9	2	7.6	10.3

Table 3.3. In vitro impedance of the two interfascicular electrodes used in the experiment, measured before and after the experiment (for electrode no. 1 the "after" measurement was made after animal five).

Time of measurement	Impedance [kΩ]			
	Electrode no. 1		Electrode no. 2	
	Ch. 1	Ch. 2	Ch. 1	Ch. 2
Before experiment	1.4	1.9	1.6	2.2
After experiment*	1.7	2.7	1.1	1.8

3.5 DISCUSSION

Existing literature on peripheral nerve interfaces has extensively investigated minimally invasive extra-neural electrodes as well as intrafascicular electrodes, which are more invasive but can provide higher selectivity. The step in-between these two with respect to proximity of the electrode to the nerve fibers, namely an electrode placement between the fascicles, has received very little attention. With this study we desired to test the concept that an interfascicular electrode could provide an alternative to other peripheral nerve interfaces, providing some level of topological selectivity and relatively easy implantation. The interfascicular electrode was inserted using blunt glass tools, which penetrated the epineurium, but not the perineurium, with ease. Once a canal had been made between the fascicles by the glass tools the electrode could be pulled into the nerve without much resistance. The electrode presented here differs from intrafascicular electrodes in the blunt insertion, avoiding penetration of the perineurium, and seems to be simpler to implant than the SPINE, which like other cuff based electrodes requires the nerve to be freed before implantation.

The *in vivo* measurements of electrode impedance show rather high electrode impedance. This may in part be because the only current path was through the perineurium and neural tissue of the fascicle with which the two contacts of the measured channel was in contact, unlike in cuff electrodes, which are often filled with saline, thus providing an alternative current path. No obvious trends were observed in the impedance across animals as the same electrode was reused, instead the impedance seems to depend on conditions in the individual animal. The highest impedance was, however, measured in animal 7 after which a lead-wire of the electrode broke. The main purpose of the impedance measurements in this experiment was to monitor that the electrode was working throughout the experiments to avoid the inclusion of data collected during electrode failure. Electrode failure occurred in one experiment because of breakage of an electrode lead. The electrode was therefore changed.

One reason for the lack of interest in interfascicular electrodes is probably the rationale that an electrode position between the fascicles will be unable to recruit fascicles selectively because of the high impedance of the perineurium, as demonstrated theoretically in the modeling study by Veltink and colleagues [27]. In this study full activation of two fascicles was obtained with high selectivity ($\hat{S}$ = 0.98±0.02, max(f) = 0.98±0.04), presumably because the passive part of the electrode shielded the fascicles from each other. These results indicate that the use of passive elements in the electrode to shield topologically separate areas of the nerve from each other could be an attractive option for achieving selective stimulation with an interfascicular electrode.

Although insertion of the electrode was smooth it could be difficult to assess electrode orientation, which was vital since the success of the electrode rested on the contacts facing directly towards the fascicles. The electrode was difficult to see in the nerve because it is rather transparent and difficult to distinguish from the epineurium when seen from the side (the contacts and the suture are the easiest elements to see through the epineurium, but the contacts cannot be seen when the electrode is correctly oriented and the suture does not provide information on orientation). The electrode was, however, observed to be correctly oriented during explantations, which is also indicated by the encouraging results. This also indicates that the electrode was successfully fixated during the experiment by the passive forces exerted on it by the fascicles and epineurium alone, despite movement of the leg in which it was implanted. However, it remains to be investigated if migration of the electrode would occur in the chronic setting.

The electrode presented in this study seems to provide a stable interface and should be safe since it does not confine the nerve to a limited space and does not penetrate the perineurium, which provides a natural protective boundary for the nerve fibers. Pressure damage could, however, still occur if movements around the nerve cause pressure to act perpendicular to the nerve, especially if the electrode material is rigid. Chronic implantation of an interfascicular electrode would obviously require biocompatible materials for electrode fabrication and perhaps also some means of fixation. For the situation dealt with in this experiment where two fascicles need to be shielded from each other polyimide might be an option since a very thin electrode could be made, which should improve the chances of the electrode having the right orientation. However, if the electrode is used in a different nerve, e.g., with multiple fascicles it would require a different electrode design, which could include sectioning the nerve into more topological chambers. Casting the electrode in silicone in a form could be an option for producing such an electrode, which also could include tiles for fixation.

The work presented here is our first attempt to design an electrode to be positioned between the fascicles of a nerve in a safe and controllable manner, and using minimally invasive procedures. As compared to this, the SPINE electrode developed by Tyler and Durand and the multigroove electrode by Koole and colleagues [33], although showing excellent selectivity properties, was an adaptation of a cuff electrode to include penetrating elements in addition to the extra-neural cuff [28]. This implies the same implant procedures as for the cuff (see above) and adds additional concerns regarding the safety of the method. Thus, penetration of the intraneural SPINE components is an incontrollable process, which may result in nerve damage, such as pressing or crushing of axons. As evidenced by the authors themselves, the 24 hours observation interval used in their study is insufficient to eliminate such concerns and chronic experiments with SPINE were not reported to date.

The main advantage of the electrode presented in the present study is the simplicity of both the electrode design and the implantation procedure. The electrode consisted of relative few components and the sleek design made it easy to pull it through the soft epineurium. Given the relative ease experienced under implantation of the electrode an adaptation of the electrode and insertion tools might even make it possible to insert an interfascicular electrode endoscopically. This could potentially provide an intra-neural electrode with sub-nerve selectivity at approximately the same cost in surgical invasiveness as percutaneous extra-neural electrodes.

3.6 CONCLUSIONS

A new interfascicular electrode design was demonstrated to provide an interesting alternative to existing nerve electrodes with a simple implantation procedure. The potential for selective recruitment of sub-populations of nerve fibers in the nerve was indicated, but requires further investigation in chronic experiments to assess the stability of the electrode orientation. Histological studies must be performed to investigate the safety of the interfascicular electrode.

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Chapter 4.

Comparison of Mono-, Bi-, and Tripolar Configurations for Stimulation and Recording with an Intra-Neural Interface

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4.1 ABSTRACT

Previous studies have indicated that electrodes placed between fascicles can provide nerve recruitment with high topological selectivity if the areas of interest in the nerve are separated with passive elements. In this study, we investigated if this separation of fascicles also can provide topologically selective nerve recordings and compared the performance of mono-, bi-, and tripolar configurations for stimulation and recording with an intra-neural interface. The interface was implanted in the sciatic nerve of 10 rabbits and achieved a mean selectivity of $\hat{S}$ = 0.98 for all stimulation configurations, while the selectivity ratio of recording configurations were in the range of 2.58-5.29 with the monopolar configuration providing the lowest and the bipolar configuration the highest recording selectivity. Interfascicular electrodes could provide an interesting addition to the bulk of peripheral nerve interfaces available for neural prosthetic devices. The separation of the nerve into chambers by the passive elements of the electrode could ensure a higher selectivity than comparable cuff electrodes and the intra-neural location could provide an option of targeting mainly central fascicles. Further studies are, however, still required to develop biocompatible electrodes and test their stability and safety in chronic experiments.

Index Terms—animal experiments, interfascicular electrode, nerve stimulation, nerve recording, peripheral nerves.

4.2 INTRODUCTION

Neural prosthetic devices utilizing stimulation of peripheral nerves are in use for multiple applications, including vagus nerve stimulation to treat epilepsy, sacral nerve stimulation to treat urinary and faecal incontinence, phrenic nerve stimulation for ventilator assistance, and peroneal nerve stimulation for correction of foot-drop [1-8]. A large variety of electrodes have been developed to provide the interface of these systems to the nerve, ranging in invasiveness from percutaneous to extra-neural, intra-neural and even regenerative interfaces [8].

The most used interface for peripheral nerve stimulation has been the extra-neural cuff electrode, which has been used for many research and rehabilitation applications for several decades, but also intrafascicular electrodes have received considerable interest over the last two decades [8, 9]. The interfascicular interface, being the intermediate stage between the cuff electrode and the intrafascicular electrode with regard to electrode placement, has received less interest.

Peripheral nerves typically consist of a number of fascicles, which (at least immediately proximal to a nerve bifurcation) have a somatotopic organization, in which the nerve fibers are grouped according to the nerve branch to which they belong [10, 11]. Interfaces that can stimulate or record from sub-regions of the nerve with a high spatial selectivity may therefore enable a single interface to control several functions, e.g., antagonist muscles, and thus reduce the need for implantation of interfaces on multiple nerves or muscles.

For stimulation it has previously been demonstrated that interface designs that separate the nerve into chambers by use of passive elements may provide high selectivity in recruitment of these chambers with respect to each other [12-14] while electrodes placed between the fascicles without passive elements would achieve very low selectivity [15]. However, the recording properties of such electrodes have not been investigated.

Interfaces that enable nerve recording provide a potential for improvement of existing and future applications of neural devices. Recording of sensory nerve signals could e.g. enable fully-implantable systems for correction of foot-drop or closed-loop muscle activation, prediction of epileptic seizures could improve the efficiency of vagus nerve stimulation for treatment of epilepsy, and estimation of bladder pressure could enable closed-loop stimulation in patients with incontinence [2, 16-19]. As with stimulation, improvements in recording selectivity could enable recording from multiple sources or increase the signal to noise by only focusing on the fascicle(s) of interest and thus remove unrelated nerve activity from other fascicles in the recording.

In the current study we investigated if placing passive elements between fascicles, as previously reported for stimulation, could enable selective nerve recording and we compared different configurations for interfascicular stimulation and recording. An intra-neural interface containing six electrodes for stimulation or recording and two reference electrodes was tested in the sciatic nerve of 10 rabbits. The intra-neural interface was hypothesized to provide a better discrimination between tibial and peroneal activation than previously reported for cuff electrodes [20].

4.3 METHODS

4.3.1 Electrodes

Cuff electrodes for recording from and stimulation of the tibial and peroneal nerves were produced according to the technique described by Haugland [21]. The cuffs were 12 mm long and contained three 1 mm wide Pt ring electrodes placed with 5 mm between the middle of each ring.

The intra-neural interface implanted in the sciatic nerve is illustrated in Figure 4.1a and shown in Figure 4.1b and c. The technique for fabricating the electrode was described in detail in [14]. The design tested in the current study consisted of a 16 mm piece of flattened 0.75/0.94 mm (inner/outer) diameter nylon tube (Portex® 800/200/175/100) with a nylon suture used for pulling the electrode into the nerve, six circular Ag-AgCl electrodes for stimulation and recording of approximately 0.45 mm diameter, and two Ag-AgCl reference electrodes of approximately 0.65 mm diameter. Three stimulation/recording electrodes were placed on each flat side of the nylon tube with 5 mm between the centers of each electrode. The two reference electrodes were placed with one on each narrow side, aligned with the center electrodes on the flat sides.

4.3.2 Surgery

Ten rabbits, weighing 3665±323 g (mean±SD), were anaesthetized with subcutaneous injection of 100 mg/kg Ketalar, 5 mg/kg Xylazine and 1 mg/kg Plegicil. Anesthesia was maintained with additional injections of half this dose 20 minutes after the initial injection and then once per hour until the end of the experiment, at which point the rabbits were euthanized with an overdose of Pentobarbital. After inducing the anesthesia, the skin of the left hind limb was anaesthetized with lidocaine and then opened in a line extending from the hip to the knee of the left hind leg. The femoral biceps and semitendinous muscles were split from each other to expose the underlying nerves. The intra-neural interface was implanted in the sciatic nerve between the muscular branch and the branching point with three electrodes facing the tibial fascicle of the sciatic nerve and the other three facing the peroneal fascicle, whereas the two reference electrodes faced the inert tissue between the fascicles. To make the incision, the suture of the intra-neural interface was threaded into a 23 gauge injection needle. The needle was inserted into the nerve, between the fascicles, and pushed along for about 2.5 cm before exiting the nerve again. The needle was then retracted and the suture used to pull the intra-neural interface into the nerve. The tibial and peroneal nerves were freed for a few cm distal to the bifurcation of the sciatic nerve and a cuff electrode was placed around each nerve. A 14 gauge injection needle was inserted subcutaneously in the back of the rabbit and used as ground electrode.

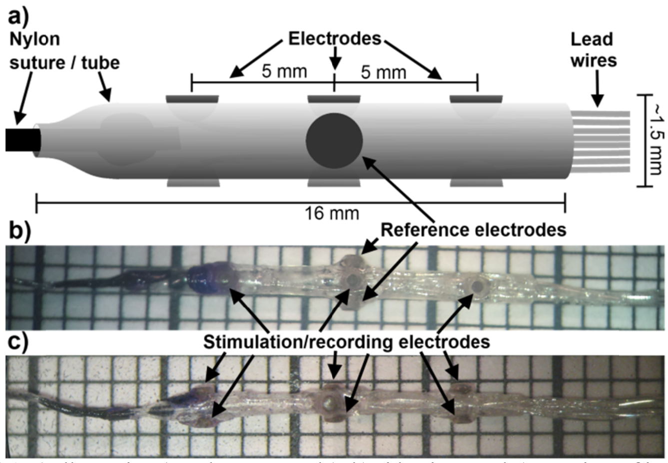

Figure 4.1. a) Illustration (not drawn to scale), b) side view, and c) top view of intra-neural interface with eight Ag-AgCl electrodes. In b) and c) the electrode is shown on mm paper.

4.3.3 Stimulation

Mono-phasic constant current square pulses of 50 µs were delivered by a SD9 stimulator with a PSIU6X isolation unit (Grass Technologies). This relatively short pulse width was chosen because of the short distance between stimulation and recording electrodes to ensure separation of the artifact and nerve volley. Recruitment curves were obtained by computer triggered stimulation with 10 single pulses at each stimulation intensity for several intensities, ranging from below recruitment threshold to above full recruitment of the first recruited nerve branch. The interval between each of the 10 stimulation pulses of the same intensity was randomized between 0.4 and 0.5 s, while each set of pulses was initiated manually. Stimulation intensity was regulated by changing the current while the pulse width was kept constant at 50 µs. Stimulation current was calculated from the linear relationship between the voltage output of the SD9 and the constant current output of the PSIU6X.

Stimulation with the cuff electrodes was bipolar with the central ring as cathode and the most distal ring as anode. Stimulation with the intra-neural interface was performed with four different configurations; 1) monopolar with the central electrode of each side as cathodes and the ground electrode as anode, 2) longitudinal bipolar with the central electrode of each side as cathodes and the most proximal electrode of the same side as anode, 3) longitudinal tripolar with the central electrode of each side as cathodes and the two outer electrodes of the same side shorted and used as anodes, and 4) transverse tripolar configuration with the central electrode of each side used as cathodes and the two reference electrodes short circuited and used as anodes.

4.3.4 Recording

Recorded nerve signals were preamplified, amplified, filtered, and further amplified using six AI402 SmartProbes and a CyberAmp 380 (Axon Instruments Inc.). The gain was chosen depending on signal amplitude. The signals were high-pass filtered using a first-order filter with -3 dB frequency of 1 Hz and low-pass filtered using a fourth-order Bessel filter with a -3 dB frequency of 10 kHz. The signals were then digitized at 16 bits resolution and 40 kHz for monopolar and 50 kHz for all other recordings using a PCI-6221 ”M series DAQ” with a BNC-2110 connector block (National Instruments) and stored on a computer for further analysis. The reduced sampling rate of monopolar recordings was due to limitations of the PCI-6221.

Cuff recordings were tripolar with the central ring used as anode and the two outer rings short circuited and used as cathodes. Recording with the intra-neural interface was performed with three different configurations; 1) monopolar with each of the three electrodes of each side used as anodes and the two reference electrodes short circuited and used as cathodes for all channels, 2) bipolar with the central electrode of each side used as cathode and the most distal electrode of the same side as anode, and 3) tripolar with the central electrode of each side used as anode and the two outer electrodes of the same side shorted and used as cathodes. A fourth configuration was created in post-processing by subtracting the average of all six monopolar channels from each channel. This is referred to as the average reference configuration in the following. Although six channels were available for the monopolar and average reference configurations only the central channel of each side were used for the selectivity evaluation.

4.3.5 Data analysis

Data analysis was performed off-line using Matlab® (The MathWorks™). A time-average was generated for each set of 10 stimuli with equal stimulation intensity and the peak-to-peak response (V_{pp}) of the direct nerve volley was calculated from this time average. For all stimulation configurations V_{pp} was normalized in each of the nerve branches with respect to the largest V_{pp} obtained during the experiment to express the response as a fraction (f) of full nerve activation.

For stimulation configurations selectivity was calculated in the same way as previously described in [14] in order to facilitate comparison with the results presented here: The selectivity index (S) was calculated for each stimulation intensity (I) as the response of the target nerve branch (b) divided by the sum of the responses of both nerve branches:

$$S_b(I) = \frac{f_b(I)}{f_{tibial}(I) + f_{peroneal}(I)} \tag{4.1}$$

in accordance with, e.g., [22], [23]. To get a single number to measure the selectivity of each configuration, it was calculated as the mean of the highest achieved selectivity in recruitment of each nerve branch while activating the branch to at least 70% of its maximum, i.e.:

$$\hat{S} = \frac{1}{2}\sum_{i=1}^{2}\max\left\{S_i\left(I\right) \mid f_i\left(I\right) \geq 0.7\right\} \tag{4.2}$$

Adapting the definition provided by Yoo and colleagues [23], a nerve branch was regarded as selectively activated in a functionally relevant way if both the criteria $S_b(I)>0.7$ and $f_b(I)>0.7$ were satisfied.

In addition, the maximally achieved f and the threshold currents required to produce 10% ($I_{10\%}$) and 90% ($I_{90\%}$) activation of the nerve branch, respectively, were obtained.

For recording, topological selectivity is related to cross-talk where the signal recorded by one channel is a sum of potentials from multiple sources and the challenge is to distinguish the source of interest from the other(s). We therefore defined recording selectivity as a selectivity ratio (SR) between the amplitudes of the desired and the undesired signals:

$$SR = \sqrt{\frac{V_{pp,Tt}}{V_{pp,Tp}} \bullet \frac{V_{pp,Pp}}{V_{pp,Pt}}} \tag{4.3}$$

where $V_{pp,cn}$ is the potential measured by channel c from nerve source n, T is the channel facing the tibial fascicle (t), and P is the channel facing the peroneal fascicle (p). To make calculation of SR possible at any point of the recruitment curve a sigmoid of the form

$$f\left(q,I\right) = \frac{q\left(1\right)}{1+e^{-\frac{I-q(2)}{q(3)}}} \tag{4.4}$$

was fitted to each recruitment curve using the build-in Matlab function nlinfit for non-linear regression. To estimate selectivity in the dynamic range of the recruitment curve the area between $I_{10\%}$ and $I_{90\%}$ was calculated for each curve: For each stimulation series the $I_{10\%}$ and $I_{90\%}$ thresholds for the recording channel facing the stimulated fascicle were calculated. The area under the fitted recruitment curve of both channels was then calculated between $I_{10\%}$ and $I_{90\%}$. To avoid scaling effects caused by differences in stimulation currents required for the different nerves, $I_{90\%} - I_{10\%} \equiv 1$ was used when calculating the areas. Applying these areas in the calculation of SR, eq. 4.3 becomes:

$$SR_{area} = \sqrt{\frac{A_{T,t}}{A_{T,p}} \bullet \frac{A_{P,p}}{A_{P,t}}} \tag{4.5}$$

where $A_{c,n}$ is the area under the fitted recruitment curve of channel c with stimulation of source n. Finally, the SR at full nerve recruitment, SR_{maxVpp}, was calculated by inserting the maxima of the sigmoid fits in eq. 4.3.

In addition, the mean of the maximum V_{pp} of the channel facing the tibial fascicle and the maximum V_{pp} of the channel facing the peroneal fascicle,

$max(V_{pp})$, was calculated for each recording configuration.

The results were compared using the independent-samples Kruskal-Wallis test to investigate if each parameter differed between the configurations. If significant differences were found the Mann-Whitney U-test was used to compare pairs of configurations. The null hypothesis was rejected at a significance level of $p \leq 0.05$. All statistical tests were performed in IBM® SPSS® Statistics. The results are presented as median (mean±SD).

Table 4.1. Results of stimulating with the intra-neural interface.

	Stimulation configurations			
	Mono-polar	**Longitudinal bipolar**	**Longitudinal tripolar**	**Transverse tripolar**
$\hat{S}$	0.98 (0.98±0.02)	0.99 (0.98±0.02)	0.99 (0.98±0.02)	0.99 (0.98±0.03)
Max(f)	1.00 (0.98±0.03)	0.96 (0.97±0.02)	0.98 (0.97±0.02)	0.97 (0.96±0.04)
$I_{10\%}$ [µA]	319 (305±77)	226 (223±67)	259 (262±76)	585 (559±214)
$I_{90\%}$ [µA]	477 (496±202)	358 (351±117)	403 (434±153)	996 (1097±567)

Table 4.2. Results of recording with the intra-neural interface.

	Recording configurations			
	Mono-polar	**Average reference**	**Longitudinal bipolar**	**Longitudinal tripolar**
SR_{area}	2.16 (2.58±1.32)	3.90 (4.13±0.92)	2.91 (4.97±6.86)	3.33 (3.32±0.43)
SR_{maxVpp}	2.19 (2.74±1.54)	3.78 (4.18±1.22)	3.07 (5.29±7.47)	3.52 (3.46±0.44)
$A_{T,t}$ [mV]	195 (206±96)	278 (294±91)	422 (428±95)	298 (306±83)
$A_{T,p}$ [mV]	43 (42±17)	40 (37±12)	83 (80±19)	47 (48±14)
$A_{P,p}$ [mV]	104 (112±70)	136 (147±73)	242 (243±82)	160 (170±76)
$A_{P,t}$ [mV]	84 (84±23)	64 (68±23)	166 (151±62)	98 (95±22)
$Max(V_{pp})$ [mV]	341 (586±142)	481 (564±137)	681 (715±144)	462 (512±134)

4.4 RESULTS

4.4.1 Stimulation

The results of stimulating with the intra-neural interface are presented in Table 4.1. Both nerve branches were selectively activated in a functionally relevant way by all stimulation configurations with no significant differences in selectivity or maximal nerve activation between the configurations ($p=0.997$ and $p=0.229$, respectively).

The $I_{10\%}$ of the longitudinal bipolar configuration was significantly lower than the monopolar and transverse tripolar configurations ($p=0.019$ and $p=0.001$, respectively), but not significantly lower than the longitudinal tripolar configuration ($p=0.174$). The $I_{10\%}$ was significantly lower for the monopolar and longitudinal tripolar configurations than for the transverse tripolar configuration ($p=0.016$ and $p=0.003$, respectively), but did not differ significantly between the monopolar and longitudinal tripolar configurations ($p=0.151$).

The $I_{90\%}$ of the longitudinal bipolar configuration was significantly lower than the monopolar and transverse tripolar configurations ($p=0.034$ and $p=0.001$, respectively), but not significantly lower than the longitudinal tripolar configuration ($p=0.174$). The $I_{90\%}$ were lower for the monopolar and longitudinal tripolar configurations than for the transverse tripolar configuration ($p=0.010$ and $p=0.001$, respectively), but did not differ significantly between the monopolar and longitudinal tripolar configurations ($p=0.326$).

4.4.2 Recording

The results of recording with the intra-neural interface are presented in Table 4.2. The SR_{area} of the monopolar configuration was significantly lower than for the average reference and tripolar configurations ($p=0.002$, $p=0.010$), but not significantly lower than the bipolar configuration ($p=0.089$). The SR_{area} of the tripolar configuration was significantly lower than the average reference configuration ($p=0.023$), but did not differ significantly from the bipolar configuration ($p=0.174$). The SR_{area} was significantly lower for the bipolar than for the average reference configuration ($p=0.005$).

SR_{maxVpp} was significantly lower for the monopolar configuration than for the bi- and tripolar configurations ($p<0.001$ and $p=0.010$, respectively), but not significantly different from the average reference configuration ($p=0.059$). SR_{maxVpp} was significantly lower for the bipolar than for the tripolar configuration ($p=0.008$), but did not differ significantly between the tripolar and average reference configuration ($p=0.705$). SR_{maxVpp} was significantly lower for the bipolar configuration than for the average reference configuration ($p=0.019$).

On average, monopolar recording provided the lowest SRs while bipolar recording provided the highest. However, the large mean SRs of the bipolar configuration were caused by a single outlier; animal 1 obtained $SR_{\mathrm{area}} = 24.47$ and $SR_{\mathrm{maxVpp}} = 26.52$, which was primarily caused by a very small A_{Pt} area. If this animal is removed the selectivity of the bipolar configuration drops to $\overline{SR_{area}} = 2.81$ and $\overline{SR_{\max Vpp}} = 2.93$, respectively. Excluding this animal from the analysis, the average reference configuration obtained the highest average selectivity with SR_{area} significantly larger than for the monopolar, bipolar, and tripolar configurations ($p=0.005$, $p=0.001$, and $p=0.038$, respectively), and SR_{maxVpp}

significantly larger than the monopolar and bipolar configurations (p=0.007 and p=0.004, respectively), but not significantly larger than for the tripolar configuration (p=0.102).

Max(V_{pp}) was significantly larger for the bipolar channel than for the monopolar, average reference, and tripolar channels (p<0.001, p=0.002, and p=0.008, respectively). The *max(V_{pp})* of the tripolar configuration was significantly larger than for the monopolar configuration (p=0.010), but did not differ significantly from the average reference configuration (p=0.059). The *max(V_{pp})* did not differ significantly between the average reference and tripolar configurations (p=0.705).

Figure 4.2 shows an example of the recruitment curves obtained from recording with the intra-neural electrode. The measured data points are plotted as triangles for the target channel and as x-es for the non-target channel and the sigmoid fits are plotted as solid lines. The areas used for the SR_{area} calculation is illustrated with the shaded areas: $A_{T,t}$ is the sum of the two shaded areas in the top plot of Figure 4.2, $A_{P,t}$ is the lower shaded area of the same plot, $A_{P,p}$ is the the sum of the two shaded areas in the bottom plot, and $A_{T,p}$ is the the lower shaded area of the bottom plot. The shown example obtained SR_{area} = 3.07 and SR_{maxVpp} = 3.13.

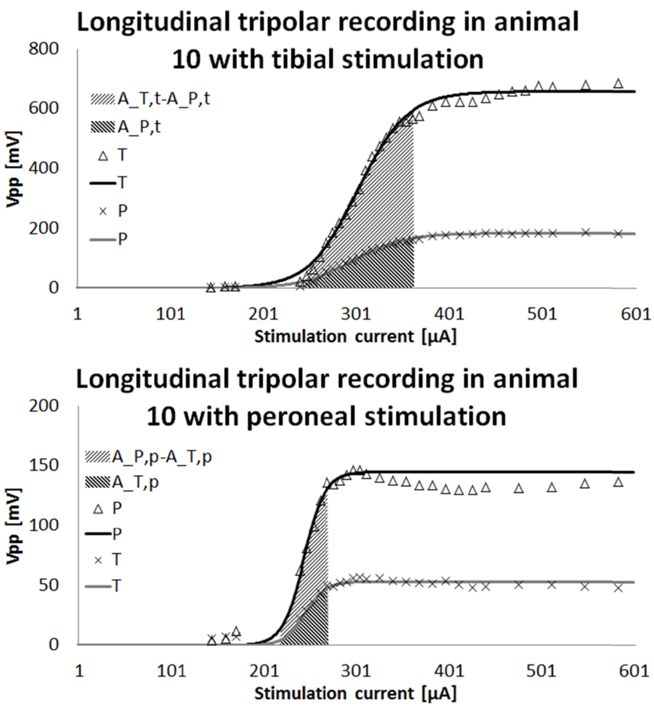

Figure 4.2. Recruitment curves obtained from animal 10 with the longitudinal tripolar recording configuration.

4.5 DISCUSSION

Existing literature on peripheral nerve electrodes focus mainly on extra-neural and intrafascicular electrodes, but studies have also indicated that electrodes placed between the fascicles can provide topologically selective recruitment of subareas of the nerve, provided that passive elements are used to compartmentalize the nerve [12, 14]. In this study, we investigated the potential of such an interface for also providing selective recording and compared some of the most common configurations, previously applied with e.g. cuff electrodes, for stimulation and recording. Compared to the intra-neural interface presented in the previous study [14], the inter-electrode distance was increased to provide a larger amplitude of the recorded signals, and the number of electrodes was increased to facilitate tripolar configurations and provide reference electrodes for the monopolar recording configuration. During preliminary studies, monopolar recording versus distant electrodes, e.g. the ground electrode, was also attempted but failed to record detectable nerve signals. Using these same reference electrodes as anodes for stimulation resulted in a transverse tripolar rather than monopolar configuration, which has previously been applied in cuff electrodes, due to the proximity of the reference electrodes to the cathode [22, 24, 25].

Stimulation with the intra-neural interface yielded a mean selectivity of $\hat{S}$ = 0.98 and recruitment of 96-98% of the target fascicle before the selective dropped below 70%, with no significant differences between any of the configurations. The selection of stimulation configuration can therefore be based on other considerations, e.g., reducing current consumption of an implant. The lowest $I_{10\%}$ and $I_{90\%}$ currents were obtained with the bipolar configuration. Although the bipolar and longitudinal tripolar configurations did not differ significantly, both the $I_{10\%}$ and $I_{90\%}$ were lower for the bipolar than the tripolar configuration in every animal. Compared to the previous study [14], neither $\hat{S}$ nor f differed significantly between the previous study and any of the configurations in this study ($p=0.997$ and $p=0.234$, respectively). As expected, the larger electrode spacing used in this study did, however, provide a lower $I_{10\%}$ current for the bipolar configuration of this study than the bipolar configuration of the previous study ($p=0.001$). An additional advantage of the longitudinal bipolar configuration is that it could be designed to provide a partly direction selective activation of the nerve by using anodal blocking to stop some of the action potentials travelling in the non-target direction [26].

Evaluating the recording configurations with the two selectivity measures, SR_{area} and SR_{maxVpp}, yields similar results with selectivity measured at full fascicle recruitment, SR_{maxVpp}, slightly higher than selectivity measured over a wide recruitment range, SR_{area}, for all configurations. Even though six channels were available for the monopolar recording configuration only the two channels from the center electrodes were used for calculating the results, rather than e.g. searching for the best electrode combination. Instead, the average of all six channels was used as a reference signal representing noise sources recorded by all electrodes. Filtering the monopolar recordings by subtracting this reference signal from each channel markedly improved selectivity to SR_{area} = 4.13±0.92 and SR_{maxVpp} = 4.18±1.22, respectively. Struijk and colleagues tested an elliptical cuff electrode with three electrodes on the tibial side and three on the peroneal side of the nerve in six rabbits [20]. Using the same SR as defined in eq. 4.3, they obtained a mean SR of 1.4 of for longitudinal tripolar recording of tibial versus peroneal stimulation.

Compared with [14], the implantation procedure was simplified slightly by reducing the implantation tools to a single needle. The needle was easy to insert in the nerve and guide between the fascicles. However, since the needle was much smaller in diameter than the electrode, the resistance faced when pulling the electrode into the nerve was larger than if the larger glass needle of the previous study was used to create a pathway through the nerve before inserting the electrode. Attaching a needle to the end of the suture of the electrode would be one way to simplify implantation of a market ready version of the interface. Such an interface should, however, use a non-conducting material for the needle and it would be preferable if the needle has about the same width as the interface to reduce stress on this during insertion. Furthermore, it would be preferable to have a blunt tip of the needle since this makes it easier to keep the tip inside the nerve, while pushing it along the nerve, and may reduce the risk of rupturing blood vessels.

While the interface described in this study neither confines the nerve to a limited space nor penetrate the perineurium, pressure damage could still occur if a very rigid interface is implanted in a location where movement may cause pressure perpendicular to the nerve such as around a joint. A chronic version of the intra-neural interface therefore needs to be developed using biocompatible materials and tested in order to evaluate the stability and safety of such electrodes. Furthermore, most practical applications would probably entail implantation of the interface in multi-fascicular nerves, rather than the two-fascicle sciatic nerve of this experiment. This would require a different design to section the nerve into more chambers. In this study, the transverse tripolar configuration performed worst of the stimulation configurations. In a multi-fascicular nerve, where each chamber might contain multiple fascicles, transverse bi- or tripolar configurations might, however, provide an option for recruiting subareas of a chamber if multiple electrodes are placed in each chamber.

4.6 CONCLUSIONS

A recently introduced intra-neural interface was tested to investigate recording properties and to evaluate potential configurations for stimulation and recording with interfascicular electrodes. Little difference was observed among the stimulation configurations, but the longitudinal bipolar configuration required the lowest stimulation current. The potential for selective recording was clear, but needs to be evaluated in a more natural environment with natural nerve activation and noise interference from e.g. muscles.

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Chapter 5.

Synthesis

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5.1 DISCUSSION

Neural prosthetic devices that interface peripheral nerves are a promising technology for rehabilitation of patients with a wide range of disorders. Muscles may, e.g., be activated directly or through reflexes to regain functional movement after stroke or spinal cord injury, bladder spasms can be suppressed and sphincter muscles contracted to restore continence, epileptic seizures may be averted, and the nerve activity that would have controlled the muscles of the natural hand could be used to control an artificial prosthesis in amputees. The interface between the nerve and the electronic system plays a key role in the development of these systems because it determines the nature of interaction and limitations of the neural prosthetic device. It is desirable to obtain the highest possible selectivity in neural control to maximize the functional gain of the device, but at the same time the risks involved with implantation cannot exceed the expected gain. The selectivity must therefore be optimized without substantial increase in invasiveness. In this respect the perineurium constitutes an important boundary; electrodes that leave the perineurium intact can be considered relative safe if care is taken to avoid compressive forces to the nerve and proper materials are used, while electrodes that penetrate the perineurium leave the nerve fibers unprotected and therefore involve a higher risk. In this thesis, three studies were conducted to investigate extra-fascicular selectivity. The transverse tripolar stimulation configuration was excellent in recruiting the small cutaneous and medium sized peroneal branch of the sciatic nerve and could be an interesting option for recruiting small and medium sized fascicles with cuff electrodes. A novel intra-neural interface was developed and shown to provide excellent stimulation selectivity and good recording selectivity, thus indicating interfascicular electrodes as an alternative to extra-neural electrodes with comparable invasiveness.

As described in the introduction, the challenge of acquiring high selectivity is quite different for stimulation and recording, respectively. Activation of a fiber requires a flow of charge across the membrane exceeding the depolarization threshold and for epifascicular stimulation the stimulation intensity must also exceed a threshold to overcome the impedance of the perineurium. Provided favorable electrode-nerve geometry this means that very high selectivity can be obtained with stimulation, at least at low intensities where current only spill into the fascicle closest to the stimulating electrode(s). Although the electrode-fiber distance also determine how much the action potential will affect the recorded compound potential, even very distant fibers will make some contribution to the compound potential making it impossible to obtain perfect selectivity and potentially reducing the selectivity substantially by the accumulative effect of a large number of active distant fibers. Stimulation and recording selectivity are therefore treated separately bellow.

5.1.1 Stimulation selectivity

The transverse tripolar configuration was able to activate 0.93±0.06 of the peroneal nerve with a selectivity of 0.98±0.01 and 0.87±0.10 of the cutaneous nerve with a selectivity of 0.95±0.08. While the transverse configuration achieved functionally selective activation of these two nerves in all nine animals, the tibial nerve was only functionally selectively activated in two of the animals. The tibial fascicle takes up at least half of the sciatic nerve in the rabbits. With an angular distance of 90º between the electrodes this means that even with optimal electrode orientation the anodes can be expected to partly reside over the tibial fascicle and thus block these parts of the fascicle. Furthermore, the cutaneous fascicle often split from the superficial posterior part of the tibial fascicle, opposite to the peroneal fascicle, i.e. with the tibial fascicle on both sides and behind the cutaneous fascicle. In such cases it would not be possible to activate the whole tibial nerve without also activating the cutaneous nerve and the two animals in which it was achieved probably represent exceptions where the cutaneous fascicle was located more to one side of the tibial fascicle. The improvement in stimulation selectivity of the transverse configuration over the longitudinal configuration was found to come at the expense of an increase in threshold current of 4.1 times. The variation in stimulation threshold was higher for the transverse configuration than for the longitudinal configuration probably reflecting sensitivity to the alignment of the cathode over the midsection of the target fascicle. The improved performance of the transverse configuration in this study compared to the previous results by Deurloo and colleagues demonstrates the interaction between stimulation configuration and cuff geometry; if the transverse tripolar configuration is used to apply a narrow field and the electrode spacing at the same time is small the resulting field will be too narrow and too superficial to fully recruit fascicles [1, 2].

However, even with a good choice of electrode layout the inability of the transverse tripolar configuration at recruiting very large fascicles and the sensitivity to cuff orientation suggests that an optimal stimulation paradigm involves testing several configurations and selecting the one that performs best for each fascicle as demonstrated by Tarler and Mortimer [3]. The transverse bipolar configuration could, e.g., be preferable in the situation where the cathode is not centered over the target fascicle, whereas the monopolar configuration or a bipolar configuration with the anode opposite the cathode could be used for stimulating large fascicles.

The intra-neural interfaces tested in study 1 and 2 showed excellent stimulation performance recruiting 96-98% of the nerve with a selectivity of 98% for all tested stimulation configurations and interface geometries. These results support the evidence from the SPINE and multi-groove electrodes that topological separation of the nerve with passive elements is an effective means of achieving high selectivity [4, 5]. Since all configurations achieved nearly perfect selectivity, the choice of stimulation paradigm can be based on other concerns. Current consumption could, e.g., be minimized by choosing a longitudinal bipolar configuration with at least 5 mm electrode spacing, which could also be optimized to restrict activation in the non-target direction. Alternatively, the monopolar configuration could be chosen for its simplicity to reduce the number of electrodes required.

5.1.2 Recording selectivity

Recording tibial versus peroneal activity with the intra-neural electrode yielded a selectivity of $SR_{\mathrm{area}} = 4.13 \pm 0.92$ for the average reference configuration. Compared to cuff electrodes, which only achieved a SR of 1.4 with a longitudinal tripolar configuration in the same setting, despite using a flat cuff geometry [6], this result is very encouraging. Further studies are, however, needed to investigate how the interface performs with natural nerve activity under realistic conditions with e.g. EMG interference from nearby muscles. It is possible that the average reference method could reduce such interference from extra-neural noise sources since distant signals should equally affect all electrodes. It is, however, possible that the difference in signal amplitude between ENG and EMG, which can be several orders of magnitude, would cause the nerve signals to be drowned in the EMG contamination. In that case the external noise might be reduced by placing a cuff around the nerve at the implant site, but this would, however, complicate implantation and increase the risk of nerve damage.

In study 2 the intra-neural interface was inserted into the nerve using blunt glass tools with a diameter of 1 mm, which was slightly larger than the interface, while study 3 used an injection needle to pull the interface suture through the nerve. The latter approach was simpler since it only required one tool, which could be attached to the suture prior to the experiment. However, the sharp tip can easily penetrate the epineurium without much force and the needle thus needs to be threaded carefully through the nerve under visual guidance unlike the blunt glass needle, which naturally follows the longitudinal path through the nerve once the tip has been inserted. Furthermore, the hole made by the injection needle in the epineurial epineurium is not large enough for the interface to pass through, and the canal made in the epifascicular epineurium is also narrower than the interface increasing the resistance of pulling the interface into the nerve. It would therefore be advantageous to use a blunt needle of similar diameter to the interface and possibly glued to the suture for insertion of the interface. The blunt needle might also reduce the risk of rupturing epineurial blood vessels during implantation.

Table 5.1. Selectivity index based only on the tibial and peroneal branches. The results are given for the longitudinal and transverse configurations separately and for the best combination of the two.

Animal	Configuration								
	Longitudinal			Transverse			Combined		
	S_T	S_{CP}	$\hat{S}$	S_T	S_{CP}	$\hat{S}$	S_T	S_{CP}	$\hat{S}$
1	0.55	0.93	0.74	0.96	1.00	0.98	0.96	1.00	0.98
2	0.52	0.78	0.65	1.00	1.00	1.00	1.00	1.00	1.00
3	0.62	0.64	0.63	0.00	0.99	0.50	0.62	0.99	0.81
4	0.66	0.96	0.81	0.00	0.99	0.49	0.66	0.99	0.83
5	0.50	0.94	0.72	0.75	0.99	0.87	0.75	0.99	0.87
6	0.53	0.88	0.71	0.99	1.00	1.00	0.99	1.00	1.00
7	0.50	0.85	0.67	1.00	1.00	1.00	1.00	1.00	1.00
8	0.63	0.81	0.72	0.00	0.99	0.50	0.63	0.99	0.81
9	0.51	0.82	0.67	0.51	0.99	0.75	0.51	0.99	0.75
Mean	0.56	0.84	0.70	0.58	0.99	0.79	0.79	0.99	0.89
SD	0.06	0.10	0.06	0.46	0.00	0.23	0.20	0.00	0.10

In order to compare the overall results obtained with the cuff and intra-neural electrodes, respectively, the selectivity of cuff stimulation was recalculated using only the responses of the tibial and peroneal nerves (see Table 5.1). On average, the cuff electrode obtained a slightly lower selectivity with the best combination of configurations than all intra-neural configurations, but this difference was not significant (p=0.847 by independent samples Kruskal-Wallis test). The effectiveness of the passive element of the intra-neural interface in constraining stimulation to one side of the nerve does, however, enable other stimulation parameters to be optimized with intra-neural stimulation. It would, e.g., be desirable to minimize the required charge injection, which could increase battery life of an implantable system, or to reduce of the number of electrodes and leads to simplify the system and reduce problems with pull on the wires. Another possibility could be to focus on also achieving direction, and possibly, fiber selectivity within the already topologically confined chamber of the nerve. It is, however, also worth noticing that the knowledge and experience that has been built up on stimulation configurations using cuff electrodes can also be applied in other interfaces. Methods to increase selectivity by field shaping, including the transverse tripolar configuration, could also be used in e.g. FINEs where the advantages of geometrical reshaping could be combined with optimal stimulation configurations. The transverse configuration did not perform well with the intra-neural interface in study 3 because each chamber only contained one fascicle. The transverse field shaping was therefore unnecessary, potentially blocking parts of the target fascicle and activating parts of the non-target fascicle at high stimulation intensity by virtual cathodes. In polyfascicular nerves it could, however, be an option to apply intra-neural interfaces with substantially fewer compartments than the number of fascicles, but to use multiple electrodes within each compartment to selectively stimulate topological subareas of the compartments.

5.1.3 Quantitative measures of selectivity

The quantification of topological selectivity of peripheral nerve interfaces is not straightforward; many different approaches have been applied in literature both in terms of how selectivity is calculated, how the results are condensed, and which method is used to measure neural output. In the studies presented here, stimulation selectivity was calculated as the signal evoked in the target nerve branch divided with the sum of signals evoked in all recorded branches. This is a rather intuitive measure since it reflects the proportion of total evoked activity in the stimulated nerve which is located to the target fascicle. Using this measure a selectivity index is calculated for each point on all sets of recruitment curves obtained during the experiments. In order to condense this to a single number that can be compared, e.g. between stimulation configurations, the maximum selectivity obtained while recruiting each branch to at least 70% of full activation was found and averaged. The selectivity could, e.g., also have been averaged over the recruitment range, but then mediocre levels of selectivity could be caused either by an evenly mediocre selectivity over the whole recruitment range or by a combination of, e.g., high selectivity in the low stimulation range combined with poor selectivity in the high stimulation range. If the interface is being tested with a particular application in mind the method used in this thesis is particularly useful; if the fraction of activation in the target branch which is necessary to achieve the desired function is estimated the selectivity of stimulation in the functional span bellow this threshold can be expected to be at least to the level of the maximum selectivity found while activating a larger fraction of the branch due to the increased risk of spill over into other fascicles as the current is increased. The disadvantage of the selectivity measure used in this thesis is that the interpretation of results needs to be based on the number of fascicles targeted in the experiment since e.g. 50%, 33%, or 25%, selectivity will correspond to a non-selective interface depending on the number of targets. This needs to be taken into consideration when comparing results obtained under different conditions. Such comparisons are, however, in any case difficult to make due to, e.g., the anatomical differences between different nerves. An alternative is to split selectivity into a benefit function and a cost function where the benefit function, e.g., represents the fraction of activation achieved in the target fascicle and the cost function represents the activity in the non-target fascicles [7-

9]. This might be a functional definition of selectivity for muscle control; if the cost function contains a threshold for the fraction of activation that produce significant muscle force the selectivity can e.g. be described in terms of how large a proportion of target muscle force can be elicited without significant activation of any other muscle.

5.1.4 Evaluation methods of selectivity

The evaluation of stimulation selectivity can be based on either ENG recorded from branches of the stimulated nerve, EMG from innervated muscles, force produced by the individual muscles (measured or estimated), or joint forces. Measures related to muscle activity, force output, and especially joint forces are very useful for evaluating interfaces in applications involving the restoration of movement. They do, however, have some shortcomings when evaluating the general properties of the interface in terms of spatial selectivity; by measuring from muscles only motor neurons are included in the evaluation and e.g. sensory fibers are ignored, the somatotopic organization of motor neurons innervating distant muscles may be uncertain, and the motor neurons innervating a certain muscle are likely to be restricted to a subarea of a fascicle. For example, Deurloo and colleagues based selectivity on the activity of four muscles; lateral gastrocnemius, soleus, tibialis anterior (TA), and extensor digitorum longus (EDL) [10]. The first two represents tibial activity while the last two represents peroneal activity. However TA and EDL are both contained in the superficial branch of the peroneal nerve and when selective activation of agonist muscle failed the analysis was further limited so that only EDL represented peroneal activity. Since the sub-fascicles, which eventually split into the superficial and deep branches of the peroneal nerve, form around the level of electrode implantation in the experiments reported in this thesis, the fibers innervating EDL will all be located within the same half of peroneal nerve and based on the general somatotopic organization of peripheral nerves [11], it is likely that the EDL fibers are further clustered within this area. Applying the method by Deurloo and colleagues for selectivity evaluation in the experiments reported here would thus have expressed peroneal selectivity exclusively in terms of the activity of large efferent fibers in a small area of the fascicle. The results would then be heavily dependent on the location of these fibers within the fascicle with respect to the location of the electrodes, the location of non-target fascicle(s) and further the location of the tested subset of fibers within these fascicle(s). By comparison, the peroneal and tibial fascicles are clearly separated proximal of the branching point, while the cutaneous fascicle forms within the tibial fascicle around the level of implantation. The branches therefore clearly represents the fascicular structure of the sciatic nerve and full activation of e.g. the peroneal nerve require activation of all efferent and afferent fibers within the whole cross section of the peroneal fascicle of the sciatic nerve.

Practical recording applications typically involve detecting a certain event, e.g., heel strike during walking. The ratio between the part of the recorded signal which represents this event and the parts of the signal which does not represent the event, i.e. the SNR, is thus decisive for the possibility to discriminate the event in the detection algorithm. When issues related to extra-neural noise are ignored, the SR appears to be a useful and intuitive measure to estimate the possibility of discriminating different topological areas of the nerve in recordings. The main challenge with this measure lies in deciding which parts of the recruitments curves are used for the calculation: For stimulation there is a simple relation between the signals evoked in the target fascicle and the signals evoked in the non-targets, i.e. they are paired to same stimuli, and the selectivity can therefore be calculated individually for each stimuli. For recording the activity of non-target fascicles is not necessarily related to the level of activity in the target fascicle. SR_{area} was therefore used in study 3 as a measure of the average performance in recording activity in the main dynamic range of 10-90% activity in the target fascicle with an average amount of activity in the non-target fascicles. The SR_{maxVpp} was also calculated for the situation where both the target and non-target fascicles were recruited to their maximum. The measure was consistently slightly higher than the SR_{area} because the noise sometimes reached the plateau of maximum activation before the signal. An additional measure that might provide useful information could be the percentage of activation in the target fascicle which results in a signal equal to that recorded with maximum activity in all non-target fascicles. This could provide a conservative estimate of the level of target activity required for confident detection of an event. In some application signal detection may, however, be improved by physiological conditions that produce non-random and sequential fascicle activation, e.g. sequential activation of synergistic groups in muscle control.

5.2 CONCLUSSION

This thesis has presented three studies exploring spatial selectivity of extra-fascicular interfaces. The transverse tripolar stimulation configuration was tested and compared to the more popular longitudinal tripolar configuration. The transverse configuration was found to perform well in recruiting small or medium sized fascicles close the electrodes while other configurations need to be applied for recruiting large or deep-lying fascicles. A novel interface was developed to test properties of interfascicular stimulation and recording. The passive elements of the interface were found to be effective at restricting stimulation current to one chamber of the nerve, regardless of stimulation configuration and electrode spacing. The results also indicated that the passive elements can facilitate selective recording of the activity within each chamber. Interfascicular electrodes are at a very early stage of development and further studies are needed to develop new interfaces and test their chronic safety and stability, as well as their sensitivity to extra-neural noise and their performance in polyfascicular nerves.

5.3 PERSPECTIVES

While cuff electrodes have been extensively investigated in chronic experiments and applied in humans the interfascicular electrodes have only been tested in acute experiments. It is therefore necessary to develop intra-neural interfaces made of biocompatible materials and to test their safety as well as stability in chronic experiments. The intra-neural interface could damage the nerve by e.g. rupturing blood vessels during implantation or by causing the nerve to be compressed against the interface during movement if forces are acting perpendicular to the nerve and the interface is rigid. If the intra-neural interface has a similar flexibility to cuff electrodes the risk of this type of compression should not be higher than for cuff electrodes, while the risk of compression due to nerve swelling is avoided by not restricting the space around the nerve, and the risk of destroying blood vessels might be reduced by blunt implantation. While the interface appeared to be fixated within the epineurial epineurium in studies 2 and 3, migration after implantation remains a concern. Chronic interfaces should therefore be designed for mechanical stability and possibly contain features, such as tiles, to ensure tissue ingrowth.

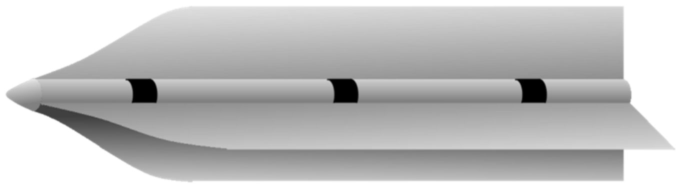

Figure 5.1. Illustration of a possible design for an intra-neural interface for use in polyfascicular nerves. In this example the interface would split the nerve into four compartments with three electrodes in each.

An intra-neural interface for polyfascicular nerves could e.g. be casted from silicone and contain four passive elements extruding from the center of the nerve after implantation to segregate the nerve into four compartments, as illustrated in Figure 5.1. A number of electrodes could be placed between the passive elements, as illustrated in Figure 5.1, for selective stimulation and recording of the fascicles within each chamber. Alternatively, electrodes could also be placed on the passive elements to enable selective stimulation of subpopulations of each compartment with transverse stimulation configurations. The interface would probably be mechanical stable after implantation since fascicles would surround it and exert pressure from all sides. Additionally, holes could be made in the passive elements to facilitate tissue ingrowth and thus chronic fixation. If the interface is casted from silicone as suggested above, difficulties can, however, be expected in obtaining an interface that is both thin and sufficiently strong to facilitate implantation and the fixation of electrodes may also provide a challenge. Furthermore, it is possible that this type of interface would be more difficult to implant if the polyfascicular nerve contains a denser layer of epifascicular epineurium than was encountered in the sciatic nerve of the studies presented here.

As described in the introduction, Tyler and colleagues recently showed in a modeling study that "directed" interfascicular stimulation potentially could provide excellent stimulation selectivity [12]. In their study stimulation were injected through cubes, which was isolated on all sides except the one facing the target fascicle. Despite the lack of passive elements separating the fascicles, perfect selectivity was obtained if the electrode was in contact with the fascicle while even electrodes located some distance away in the epineurium achieved better selectivity than extra-neural electrodes. These results indicate that compartmentalization of the nerve is not necessary if the purpose of the interface is selective stimulation, which provides more flexibility in the design options. To exploit this, an interface could, e.g., be adapted from transverse intrafascicular polymer electrodes. For interfascicular stimulation it would probably be advantageous if the width of the interface and the size of the electrodes are increased as compared the dimensions used for intrafascicular stimulation. Furthermore, a blunt needle should be used during implantation instead of the tungsten needles used for intrafascicular stimulation to ensure an epifascicular incision path.

In addition to the possibilities for spatially selective stimulation, intra-neural interfaces could be advantageous to extra-neural electrodes if the fibers of interest are located in the center of a polyfascicular nerve. In such a case stimulation with a cuff electrode would activate all the superficial fascicles before the central ones would start to be activated (although it is possible to block the superficial fascicles it would require high stimulation amplitudes). Recording of the same fibers with a cuff electrode would also be hampered by the interference of neural noise from the superficial fascicles closer to the electrodes. Although an electrode placed in the center of the nerve might not have high selectivity, stimulation would predominately recruit central fascicles before spilling over into more superficial fascicles and an active fiber in the center of the nerve would produce a higher potential at the electrode than an active fiber further away. In addition to this, cuff electrodes needs to be made at a larger diameter than the nerve to avoid nerve damage as the nerve swells after implantation. Although connective tissues would also form around an intra-neural electrode the distance to the nearest nerve fiber would presumably be considerably smaller than for cuff electrodes. An electrode design for this application could e.g. be similar to the percutaneous electrodes by Medtronic, but with smaller dimensions and tiles for fixation in the nerve and tissue ingrowth. If such an interface is designed to place multiple electrodes along the axis of the nerve it could furthermore be designed for direction (and fiber) selective stimulation and/or recording using the techniques developed for cuff electrodes.

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