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Temporal Modulation of the Response of Sensory Fibers to Paired-Pulse Stimulation

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Abstract—Multi-channel nerve cuff electrode arrays can provide sensory feedback to prosthesis users. To develop efficacious stimulation paradigms an understanding of the impact that spatio-temporal patterns can have on the response of the sensory fibers is crucial. We used experimental and modelling methods to investigate the response of nerve fibers to paired-pulse stimulation. Nerve cuff electrode arrays were implanted for stimulation of the sciatic nerves of rats and the sensory compound action potentials were recorded from the L4 dorsal root. A model of the nerve cuff electrode array and sciatic nerve was also developed. The experimental and modelling results were compared. Experiments showed that it took 8 ms for the sensory fibers to completely recover from a conditioning stimulus, regardless of the relative position of the electrodes used for stimulation. The results demonstrate that the electrodes on the cuff cannot be considered independent. Additionally, at the stimulus level used here, there is a large overlap in the fibers that were activated by the different electrodes. If a stimulus paradigm considered the electrodes as independent, stimuli from the different electrodes would need to be interleaved, and the intervals between the stimuli should be greater than 8 ms.

I. INTRODUCTION

A sense of touch is vital when it comes to interacting and experiencing the world around us [1], [2]. In the case of limb difference (loss or absence of limb), mechatron hands have advanced over the past decades, however, the addition of sensory perception is still in its infancy [2]. Providing prosthetic hand users with sensory perception has been shown not only to greatly improve control of the hand, but also promote a sense of embodiment and reduce phantom limb pain [1], [3]. Substituting sensation with external devices has been shown to help in laboratory settings, however, none of these devices have been widely adopted [2]. Electrical stimulation of the nerves in the residual limb has the potential to provide sensory information from a prosthetic hand [4]–[10].

A number of devices that interface directly with the peripheral nerves have been developed to provide electrode stimulation [3], [11]. These neural interfaces include intrafascicular electrodes that penetrate the nerves (TIMEs [6], [12], [13], LIFEs [14], [15]) and cuff electrode arrays that wrap around the nerve without penetrating it (Spiral cuffs [1], [16], FINEs [17], [18]). Generally, nerve cuff electrode arrays do not stimulate as selectively as intrafascicular electrode arrays. However, they have been shown to provide a stable interface with the nerve, and to evoke realistic sensory sensations [1].

Testing of multi-channel cuffs in humans has mainly focused on the ability to modulate the perceived sensation by tuning the frequency, amplitude, or pulse width delivered by a single electrode [1], [2], [4], [6]. Spatio-temporal patterns of electrical stimulation delivered from multiple electrodes has the potential to provide patients with different sensations experienced concurrently. In cochlear [19], [20] and retinal implants [21] interactions between electrodes can greatly alter the resultant percept. For example, stimulating the nerve with two electrodes simultaneously results in significant interactions between adjacent electrodes due to the vector summation of their electric fields [20], [22], [23]. As a result, cochlear implants employ strategies that interleave stimuli to avoid electrode interactions [19], [20]. Additionally, even after the electric field applied by an electrode has been removed, the nerve still needs to recover [24]. This can result in changes to the response of nerve fibers to the same stimulus even if stimuli are applied asynchronously. Therefore, it cannot be assumed that asynchronous stimuli will produce independent percepts and stimulus paradigms that consider electrode channel independence will need to carefully consider the timings between sequential stimuli. In stimulus paradigms that move beyond electrode channel independence, interactions between electrodes could be taken advantage of [20]. This is the case in current steering, also known as field shaping, where the electric fields generated by two or more electrodes stimulated simultaneously are combined to target a specific population of fibers within the nerve [16], [25]–[27]. These studies show that knowledge of the spatio-temporal interactions of an electrode array is essential for developing effective patterns of stimulation in a sensory prosthesis.

Spatio-temporal interaction studies to date in peripheral nerves, e.g. the sciatic nerve, have been limited to their effects on motor fibers, as the response of these fibers can be inferred from twitch force [28]–[30] and ankle torque [17], [31] measurements. These studies have shown that both intrafascicular [28], [29], [32] and nerve cuff electrode arrays [16], [17], [33] can be used to selectively stimulate motor fibers from different branches of the sciatic nerve. In addition, they have
shown that through interleaving multi-site stimulation, fatigue-resistant and ripple-free motor responses can be generated [30], [33]. Due to the difficulty of isolating sensory fibers, little work has been done to determine if sensory fibers will behave in the same way. However, we expect that sensory fibers will behave in a similar fashion to motor fibers, albeit with a lower threshold to generate an action potential [1].

Modelling of the electric fields generated in combination with simulations of axon populations are invaluable in the study of spatio-temporal interactions. This is because examination of a large range of parameters would not be feasible to test in clinical or preclinical studies [34]. Models allow for the effects of the location of the electrode contact in relation to fascicles or nodes of Ranvier to be investigated [31], [35].

This would be near impossible to test in-vivo. Models can also provide greater insight into what state both the fast and slow acting voltage-gated sodium channels are in [36].

We examine how spatio-temporally patterned stimulation of the sciatic nerve affects the sensory responses on the L4 dorsal root. We compare the results from laboratory experiments and computer modelling. We characterize the effects of varying both the delay between sequential stimuli, and the spatial location of the electrodes on the compound action potentials (CAPs) generated at L4 dorsal root. We address two questions: (1) whether or not stimulation from different electrodes on the multi-channel cuff could be considered independent; and (2) if the electrodes cannot be considered independent, what inter-stimulus interval is required so that these interactions do not have an effect on the response of the sensory fibers.

II. METHODS

We describe the experimental and simulation studies used to investigate the spatio-temporal interactions of stimuli that were delivered with a multi-channel cuff electrode array.

A. Animal Preparation

All procedures were performed under appropriate licences issued by the UK Home Office under the Animals (Scientific Procedures, Act, 1986) and were approved by the Animal Welfare and Ethical Review Board of Newcastle University.

Four Sprague Dawley rats were used in this study weighing from 400 to 475 grams. Anaesthesia was induced in a box with 3\% isoflurane in Oxygen. After anaesthesia was induced, the animal was moved onto a surgical table where anaesthesia was maintained through a mask. To help maintain anaesthetic depth, a subcutaneous injection of meloxicam was given at a dose of 1 mg/kg. Anaesthetic depth was assessed through monitoring of the animal’s heart and breathing rates and its responses to noxious toe pinches. Anaesthetic level was adjusted as needed throughout the procedure. Fluids were delivered through a tail vein cannula at 0.2 ml/hour (20 ml 0.9\% NaCl and 5\% glucose, with 0.05 ml KCl).

An incision in the skin was made over the L2 to L6 vertebrae (Fig. 1a). Muscle tissue was thoroughly cleared from around the L6 spinous process for placement of the ground electrode. The L5 spinous process was left in place and a tungsten wire was wrapped around it to act as a ground electrode for recordings. The wire was then secured with dental acrylic. To expose the L5 dorsal root a restricted lateral-medial laminectomy was performed. The opening was then covered in saline and gauze to keep the tissue wet while the rest of the surgery was carried out.

A concentric nerve cuff electrode (Microprobes for Lifescience, USA) was implanted on the proximal side of the sciatic nerve following procedures described previously [37], [38]. Briefly, an incision was made in the skin approximately 0.5 cm caudal and parallel to the right femur. The two planes of the biceps femoris muscle were dissected to expose the sciatic nerve (Fig. 1a). The nerve was freed from the surrounding tissue in preparation for implantation of the cuff electrode array. Two tungsten wire hooks were placed in the tibia's anterior (TA) muscle to monitor electromyography (EMG).

The cuff electrode arrays had an inner diameter of 1 mm with sixteen channels arranged in four rings of four contacts (Fig. 1b). Each ring was separated by 0.75 mm. Each contact was made from 100 \mu m platinum wire and had a surface area of approximately 0.0629 mm$^2$. All other electrodes were made in-house from tungsten insulated wire of 125 \mu m diameter (Advent Research Materials, UK).

After the cuff electrode array was secured with Kwik-Cast (World Precision Instruments, USA), the muscles and skin were closed above the nerve cuff with tissue glue and the gauze and saline were removed from the opening above the spinal cord. The dura was cut to expose all the spinal roots. The L5 dorsal root was identified after locating the L4 dorsal root ganglion. The L4 dorsal root was then separated from the others, lifted and placed across tungsten wire hook electrodes using a glass hook. The tungsten hooks were separated by approximately 1 mm, and connected to form a bipolar pair with an electrode located 2 mm away (Fig. 1c). The root was placed over three hooks. Only one bipolar channel recorded, if it was not long enough to be placed over the four hooks without stretching. Otherwise, the root was placed over four hooks and two bipolar channels were recorded. The opening was then filled with paraffin oil to insulate the recording electrodes from the surrounding tissue.

B. Neural Recording

CAPs were recorded using bipolar hook electrodes placed on the L4 dorsal root. While the rat sciatic nerve contains sensory fibers that project to the dorsal root ganglia from L3 to L6, we chose to record from L4 due to space restrictions, and that 98-99\% of sciatic nerve neurons project to either L4 or L5 [39]. However, this does mean that we may not have been capturing the complete effects of the stimulation. The electroneuographic (ENG) signals were bandpassed filtered between 10 and 5000 Hz, and amplified using a differential amplifier (A-M systemsTM, USA). The output from the amplifier was connected to an analogue input of a Cerebus Neural Signal Processor (Blackrock Microsystems, USA) and sampled at a rate of 30 kHz.

C. Neural Stimulation

Stimuli were delivered to the sciatic nerve through each electrode on the 16-channel cuff electrode array using a Cere-
tim R96 (Blackrock Microsystems, USA). The experiment was conducted in two parts. First, the threshold current required to elicit a CAP that could be identified on a single-trial basis on an oscilloscope was found. The stimuli used to determine threshold and all subsequent stimulations were monopolar, biphasic, cathodic first, current pulses with a pulse width of 200 µs and an inter-pulse-interval of 100 µs. The current return path was a tungsten wire placed in the skin, above the sciatic nerve. All parameters were kept constant except for the current amplitude. The current amplitude was initially set to 40 µA and stepped up or down at intervals of 5 µA. When close to the threshold current, the step size was reduced to 1 µA. After finding threshold a current that generated the maximum CAP was found by finding a current that when the amplitude was increased further, no detectable increase in CAP could be seen. The current was then increased beyond this level to ensure that the maximum CAP was recorded. Each electrode was stimulated 10 times at threshold, 120% of threshold and at a current amplitude that generated the maximum response. The recordings were averaged across the trials. In Animal 2, electrode 14 was broken. This electrode was removed from all animals so that equal comparisons could be made.

For part 2, the nerve was stimulated with a pair of electrodes using current amplitudes of 120% of threshold. A paired-pulse stimulation paradigm was used where a first “conditioning” pulse was sent from one electrode, \(e_n\), \((n = 1, 2, ..., 12)\). A second “test” pulse was then sent from a second electrode that could be in one of five possible locations relative to the first electrode \((e_n, e_{n+1}, e_{n+2}, e_{n+3} \text{ or } e_{n+4})\) as illustrated in Fig. 1b. These five possible locations are described in more detail in Table 1 and were labelled as: “origin”, 90 degrees, 180 degrees, 270 degrees and 0 degrees. In Animal 1, the origin location was not tested.

The time period between the conditioning and test pulses was varied from 0 to 10 ms in 1 ms steps. Preceding the conditioning pulse by 0.5 seconds, a single “normalization” pulse, identical to the test pulse was delivered, as illustrated in Fig. 1d. The normalization pulse was used to normalize the CAP to account for any changes in the nerve’s responsiveness over time. Each stimulus combination was repeated 10 times.

D. Analysis of the ENG recordings
The ENG recordings were analysed offline in MATLAB\textsuperscript{TM}. In the interest of consistency between all animals, only one bipolar channel was used for data analysis. A synchronisation signal from the Cerestim was used to segment the data. The recordings from the 10 repeats for each stimulus combination was then averaged over a period of 0 to 20 ms, where 0 ms corresponded to the detection of the rising edge of the synchronisation signal. The peak-to-peak response of the CAP was calculated by first finding the minimum and maximum potentials recorded over the time period of 1.5 to 3 ms after the initiation of the test pulse. The minimum potential was subtracted from the maximum. The time period was chosen to contain the entire CAP and exclude the stimulus artefact.

E. Simulations
A semi-infinite nerve was modelled with a length of 60 mm in the \(z\)-direction and simulated using 64 FEMS developed by SimNeurex LLC (Gainesville, FL). The nerve contained
The conditioning and test pulses are delivered by electrodes that are separated by 270 degrees. They could be located on the same ring or on adjacent rings.

<table>
<thead>
<tr>
<th>Label</th>
<th>Description</th>
<th>Conditioning</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>origin</td>
<td>The conditioning and test pulses are delivered by the same electrode</td>
<td>$\varepsilon_n$</td>
<td>$\varepsilon_n$</td>
</tr>
<tr>
<td>90 degrees</td>
<td>The conditioning and test pulses are delivered by electrodes that are separated by 90 degrees. They could be located on the same ring or on adjacent rings.</td>
<td>$\varepsilon_n$</td>
<td>$\varepsilon_{n+1}$</td>
</tr>
<tr>
<td>180 degrees</td>
<td>The conditioning and test pulses are delivered by electrodes that are separated by 180 degrees. They could be located on the same ring or on adjacent rings.</td>
<td>$\varepsilon_n$</td>
<td>$\varepsilon_{n+2}$</td>
</tr>
<tr>
<td>270 degrees</td>
<td>The conditioning and test pulses are delivered by electrodes that are separated by 270 degrees. They could be located on the same ring or on adjacent rings.</td>
<td>$\varepsilon_n$</td>
<td>$\varepsilon_{n+3}$</td>
</tr>
<tr>
<td>0 degrees</td>
<td>The conditioning and test pulses are delivered by electrodes that are separated by 0 degrees and are located on adjacent rings.</td>
<td>$\varepsilon_n$</td>
<td>$\varepsilon_{n+4}$</td>
</tr>
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Two fascicles based on histology obtained from the proximal end of the rat sciatic nerve [40]. The larger fascicle was 0.61 mm in diameter while the smaller fascicle was 0.35 mm. Both fascicles were modelled as an endoneurium contained within a perineurial sheath that was equal to 3% of the fascicle diameter [41]. A nerve cuff electrode array was centered on the nerve.

The cuff electrode array was modelled as a silicone sleeve with inner diameter of 1 mm and 4.25 mm in length, with a 0.2 mm thick wall, approximating the array used in experiments. A total of 16 platinum electrodes were included, simulating the used cuff electrode array. Adjacent rows of electrodes were 0.75 mm apart. The diameter of each electrode was 100 μm. The arc-length of each electrode was varied from 0.2 to 0.5 mm in 0.1 mm steps (Figure 1E). A 1 mA cathodic current was applied to each electrode independently. The fields generated by multiple electrodes were summed. The nerve-cuff complex was centred in a saline volume measuring 100 × 100 × 200 mm³. The outer borders of the saline were set as sinks. Electrical conductivities of all materials can be found in [18].

Using the DC Conduction solver with a stopping threshold of 0.5% error and an adaptive mesher, each model required approximately 5-10 minutes and 100,000-200,000 tetrahedra to converge to a solution. The potential (voltage) field within each fascicle was exported to MATLAB. The exported fields were used to linearly interpolate the extracellular potential along axons. Specifically, 1000 axons were randomly positioned within each fascicle. Each axon contained 41 nodes of Ranvier. The diameter of the axons ranged from 4 to 15 μm with a bimodal distribution with peaks at 4 and 9 μm [42].

We simulated the axons once the extracellular potential was interpolated along the randomly positioned and sized axons. The double cable axon model was used [43]. This model is based on a mammalian motor axon, rather than sensory fibers. For the experiments we used a pulse amplitude that was 120% of the threshold. For the simulations we assumed that at threshold 10% of the axons fired an action potential. Thus, we first determined the stimulation threshold for every axon. Stimulation thresholds were then sorted in ascending order. The threshold was determined as the pulse amplitude required to generate an action potential in 10% of the axons. We then simulated stimulus pulses at 120% of the threshold. The time delays between each stimulus pulse were stepped from 0 to 10 ms in steps of 1 ms. This sweep was repeated for every combination of the 16 electrodes at the five possible angles, within the 4 families of electrode lengths, and for every axon, totalling 1024 possible combinations for each axon. Additionally, axons were simulated with only one active electrode to isolate the timing characteristics of an action potential produced by that electrode during post-processing.

All simulations were run at the Ohio Supercomputer Center [44]. Each combination of parameters was run in parallel on a 28-core machine and required three hours of wall-time per electrode combination for a total of 768 hours of computation time. Symmetry of the electrodes within the cuff array allowed us to eliminate half of the simulations, considering only the combinations of electrodes in the first and second row with any of the other electrodes. To reduce the amount of storage from the simulation results, the voltage at each time point was only stored for every fifth node of Ranvier.

### F. Analysis of Simulated Data

The output from the simulations comprised the voltage against time data for every axon and electrode parameter combination. The voltage values represented the extracellular voltage at every 5th node of Ranvier in 5 μs time steps for the duration of the stimulus. In the case where the pulse amplitude was below threshold, a zero was stored to indicate that no action potentials would have occurred. In the case where an action potential was generated in an axon (from here on called an active axon), the peak voltage was stored. This analysis was repeated for every axon for each of the electrode combinations. To investigate the effect of a conditioning pulse on the response of the fibers, we counted the number of active axons in response to the second (test) pulse and compared this to the number of active axons when a single pulse was delivered on the same electrode, i.e. the one that delivered the test pulse, without a condition pulse. The ratio between active axons with and without a conditioning pulse was calculated for each time delay.

III. RESULTS

The effect of the spatio-temporal interactions between electrodes on the recovery of the response of sensory fibers was investigated both experimentally and with modelling. In all four animals the CAPs were recorded at the L₄ dorsal root in response to stimulation of the sciatic nerve. A paired-pulse paradigm was used to investigate the recovery of the response of sensory fibers, where 11 different temporal spacings and 5 different spatial positions were examined in all animals except Animal 1, where the origin spatial condition was not tested.
An example of a maximum response and a 120% response is presented in Fig. 2b. The maximum response was not recorded in Animal 1. The ratio of the peak-to-peak of the CAP recorded at 120% to the peak-to-peak of the CAP recorded at maximum current amplitude was calculated in percent and is plotted for each animal in Fig. 2c. The mean ratios were 17, 13, and 8 percent for Animals 2, 3, and 4 respectively.

B. Temporal separation of pulses

The ENG of the L_4 dorsal root was recorded in response to biphasic cathodic first pulses applied to the sciatic nerve. An example of the ENG recordings made is shown in Fig. 3A, where the interval between the conditioning and the test pulse were varied. In this representative recording, when the inter stimulus interval was 1 or 2 ms, the recorded CAP does not differ from the recordings made at other time intervals. This indicates that no detectable CAP was generated at these two intervals and the peak at 1 ms is due to the conditioning pulse.

The peak-to-peak value of the compound action potential was measured. The box plot in Fig. 3b shows the representative results for one representative animal, Animal 3. For each animal the mean peak-to-peak of the CAP recovered to within 90% of the normal response after about 8 ms. Results from all animals are presented in the supplementary material.

C. Spatial separation of pulses

The relative position of the two electrodes used to deliver the stimuli was varied in addition to the interval. The two electrodes could have five positions relative to each other: origin, 90 degrees, 180 degrees, 270 degrees or 0 degrees. In Fig. 3, the data has been pooled into groups based on the relative position of the electrodes to each other and the mean ± the standard error plotted for each stimulus interval. In all animals regardless of the electrode positions a similar trend was seen. The CAP generated by two electrodes that delivered stimuli simultaneously was much larger than that generated by a stimulus delivered by a single electrode. The peaks of the CAPs measured in response to the test pulse delivered 1 to 7 ms after the conditioning pulse are reduced. Representative results for Animal 3 are shown in Fig. 3c. Results from other animals are in Supplementary Materials.

D. Comparison of the experiment to the simulation results

Figure 3d shows that the results of the finite element study were similar to the results from the experiments. There is, however, one noticeable difference. In the model, the fibers recovered faster than in the experiments. The model showed that the fibers completely recovered their response after about 5 ms; almost half the time seen in the experiments. All electrode arc-lengths tested showed similar results.

Comparing the simulation results in Fig. 3d to the results in Fig. 3c, we observe that at 1-2 ms there is a larger reduction in the response of the nerve fibers in the model than the experiment. However, this is most likely due to how this was measured in the experiments compared to the model. In the experiments, the peak-to-peak value of the signal was

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calculated and normalised, whereas in the model, the percent of axons that generated an action potential can be directly determined. In some cases in the experiment at the 1 and 2 ms inter-stimulus-intervals, the nerve was still responding to the conditioning pulse, thus the response of the nerve to the test pulse would be overestimated. An example of this can be seen in Fig. 3a. At 1 and 2 ms, all inter-stimulus-intervals traces follow a similar trajectory, indicating the neural response at this time point is due to the conditioning pulse.

IV. DISCUSSION

We measured the response of sensory fibers to a paired-pulse paradigm, and associated them with spatio-temporal interactions between electrodes. While we only recorded the neural response from L4 and thus were not capturing all the effects of the stimulations applied to the sciatic, inferences can still be made. A finite element model was used to further elucidate what was happening in the nerve. Experimental results showed that regardless of the relative position of the electrodes, the peak-to-peak of the CAP was reduced when a conditioning pulse was delivered less than 8 ms before the test pulse. When the test and the conditioning pulse were delivered by the same electrode, the largest reduction in the peak-to-peak of the CAP was observed. This was in line with the simulation results were collected with a current amplitude that was 120% of the threshold for a given electrode. All simulations results used a current amplitude that was 120% of threshold assuming a threshold pulse generated an action potential in 10% of the axons.

The thresholds found here to generate a detectable sensory CAP were on average lower than those found previously to generate a visually detectable muscle twitch [22]. This is in agreement with studies in humans, where sensory percepts are produced before muscle activity is recorded [1]. The maximum current used throughout the experiments was 200 μA, this corresponds to a k-value of 0.4 for the electrodes used, well below the safe threshold of 1.5, as suggested by Shannon [47].

A. Selectivity of Electrodes

Interactions varied as a function of temporal spacing between the two pulses. The relative position of the two electrodes used to deliver the stimuli had little influence on the response of the sensory fibers to the delivered stimuli. Therefore, regardless of the relative position of the two stimulating electrodes, the stimulations were generating action potentials in an overlapping subset of axons.

One explanation for the selectivity of the stimuli from different electrodes being so poor comes via a study by Leventhal et al. [35]. Using finite element modelling and experiments, Leventhal et al. [35] demonstrated that at low current levels, selectivity can be reduced in comparison to higher currents due to the same group of large diameter fibers being recruited first by different electrodes [35]. At higher currents, they found that smaller diameter axons closer to the individual electrodes were recruited, increasing selectivity up to a point where the fields from the different electrodes begin to overlap greatly, and selectivity decreases. While, we did not test different current levels, our results suggest that all the electrodes tested appear to be recruiting the same small subset of fibers. This indicates that the current
amplitude used within our study may be below that required for selective stimulation of smaller fibers. Furthermore, the study by Leventhal et al. [35] also showed that selectivity of electrodes could be improved by aligning them with the different fascicles. Given the difficulty of aligning the nerve cuff electrode arrays with fascicles during surgery, in both our finite element modelling and animal studies, we did not align the electrodes with any of the fascicles. Therefore, it is unlikely that our nerve cuff electrode arrays would be in the optimal position for selectivity. We measured the CAP in response to different stimuli. It is not known if the measured CAP would correspond to a percept in the animal or, if it did, if stimuli delivered by the different electrodes would be identified as different perceptions.

B. Implications for Sensory Feedback Prostheses

For a sensory feedback prosthesis, providing patients with information about discrete events may be more beneficial than supplying the patient with information continuously [48]. If this discrete event-driven sensory feedback control policy was to be implemented in an invasive prosthesis, then different electrodes on a multi-channel cuff array could be used to signify different events. Such stimulus paradigms would need to make sure the inter-stimulus interval was at least 8 ms apart to reduce the propensity for spatio-temporal interactions between electrodes to influence the resultant perceptions. Although, the 8 ms interval here corresponds only to the recovery of the sensory fibers, research is needed to determine the shortest time delay at which humans can detect two different stimuli.

C. Limitations

The results of this study are limited to one stimulus amplitude, delivered from electrodes that are relatively close (less than 1 mm apart) on a cuff. Both stimulation amplitude and position will effect the selectivity of the stimulation [35]. Increasing the distance between the rings on the cuffs, may increase selectivity. Secondly, the pulse amplitude was chosen so that we could visual detect a CAP on every trial. However, decreasing the pulse amplitude closer to threshold would likely also alter the selectivity. Both of these factors may also influence the time it takes for the nerve fibers to recover from the application of the pulse. Further work is needed to see what effect these two factors would have. Thus, the stated recovery time of 8 ms here may significantly differ if the geometry of the cuff or the pulse amplitude was changed.

V. CONCLUSION

For an limb prosthesis to deliver complex sensory information, spatio-temporally patterned stimuli can be used. The results of this study demonstrate that spatio-temporal interactions need to be carefully considered in the design of efficacious stimulation protocols. Stimuli from different electrodes on the multi-channel cuff tested here could not be considered as independent, regardless of their relative positions on the cuff. If a stimulus paradigm considers the electrodes as producing independent percepts, the stimuli will need to be interleaved to reduce the likelihood of electrode interactions affecting the resultant percepts. This study highlights the need for further neuroscience and modelling studies to help elucidate the influence that different stimulus paradigms would have on the resultant percepts experienced by a person.

VI. DATA ACCESS STATEMENT

Data supporting this publication is available under an ‘Open Data Commons Open Database License’. Additional metadata are available at: http://dx.doi.org/10.17634/154300-105

VII. CONFLICT OF INTEREST

Matthew Schiefer is the owner of SimNeurex LLC.

REFERENCES


Supplementary Material

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1 Overview

This document provides the supplementary material to support the manuscript entitled “Temporal Modulation of the Response of Sensory Fibers to Paired-Pulse Stimulation” submitted to IEEE Transactions on Neural Systems and Rehabilitation Engineering.
1.1 Temporal Spacing Between Pulses

Figure 1: Box plots showing the normalized peak-to-peak value of the compound action potential as the interval between the conditioning and the test pulse is increased. Results are shown for all four Animals: (a) Animal 1, (b) Animal 2, (c) Animal 3 and (d) Animal 4. The red line in the center indicates the median, the bottom and top edges of the box indicate the 25th and 75th percentiles, the whiskers extend to the most extreme data points, and the red crosses indicate outliers. \( n = 55 \) for each time interval in each animal. This illustrates that similar results were obtained for the same experiment in four different animals on four different days.
1.2 Circumferential Spacing Between Electrodes

Figure 2: The mean ± the standard deviation of the normalized peak to peak for each electrode circumferential position. Results are shown for all four Animals: (a) Animal 1, (b) Animal 2, (c) Animal 3 and (d) Animal 4. \( n = 11 \) for each time interval for each position in each animal. This illustrates that similar results were obtained for the same experiment in four different animals on four different days.