Seminar: Peripheral Nerve Interfaces

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***Abstract*—Peripheral nerve interfaces are one of the most important inventions in the field of bioelectronics, allowing for direct communication between the peripheral nervous system and external devices. These are being used at the forefront of applications such as prosthetics, pain management, and neural rehabilitation. This report provides an overview of PNI, describing its biological basis, types, hardware components, data processing techniques and clinical applications in detail. While holding much promise for transformation, long-term biocompatibility, signal reliability, and scalability continue to be some of the main challenges facing PNIs. This report underscores the importance of interdisciplinary efforts to address these barriers and advance PNIs toward widespread clinical application.**

I Introduction

Neurointerfaces for the peripheral nervous system are a modern and promising area of research in the field of medicine and technology. Peripheral nerves, unlike the spinal cord and brain, do not have protection in the form of bones covering them, as a result of which they are more likely to be injured, but also more accessible for invasive manipulations [1].

II Biological background

The structure of a peripheral nerve can be described as a complex organization where myelinated and unmyelinated nerve fibers of varying diameter and function are tightly packed together in fascicles (Figure 1). A specialized sheath-like structure called the perineurium(p) forms the outer boundary of each fascicle. The perineurium is the primary source of mechanical strength for the nerve trunk and is comprised of up to 15 dense layers of cells and collagen. In addition to nerve fibers inside each fascicle there is the endoneurium(end) which consists of Schwann cells, immune cells, capillaries, and a matrix of collagen and other connective tissue fibers that support nerve fibers. Finally, holding multiple fascicles together to form the outer bundle of a compound nerve trunk is the epineurium(epi).

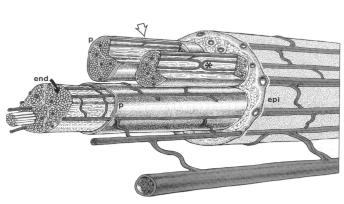

Fig. 1: Peripheral nerve anatomy [2]

The peripheral nervous system transmits control (efferent) and informational (afferent) signals between the central nervous system and other parts of the body. In cases of neurological or other dysfunction caused by injury or disease, due to the relative accessibility of the peripheral nervous system, they are an attractive target for therapeutic intervention [2]. Implantable interfaces represent an attractive solution for direct access to peripheral nerves and provide increased selectivity for both recording and stimulation compared to their non-invasive counterparts. However, the long-term functionality of implantable PNIs is limited by tissue damage that occurs at the implant-tissue interface, and therefore strongly depends on the properties of the material, biocompatibility and implant design. Current research is focused on the development of mechanically compatible PNIs that adapt to the anatomy and dynamic movements of nerves in the body, thereby limiting the reaction of a foreign body [3].

III Types of PNIs

The first Peripheral Nerve Interfaces emerged in the late 1960s, consisting of simple wires or metal foil insulated with silicone rubber. These early interfaces were primarily applied to the phrenic nerve for diaphragm stimulation and to sacral roots for bladder control. Since then, the range of applications has expanded, revealing specific opportunities and challenges associated with different nerves and target functions in the peripheral nervous system (PNS) [3].

The main types and categories of PNIs can be divided into extraneural, interfascicular, intrafascicular, and regenerative (Figure 2).

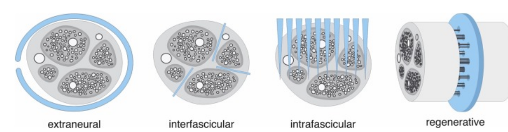

Fig. 2: Main types of PNIs [2]

Extraneural PNIs are positioned outside the nerve, which can preserve the nerve's integrity by maintaining a greater distance from individual fibers. However, extraneural PNIs can damage nerves through compression, disrupting nutrient transport and metabolism. The most common example of this type, extraneural cuffs (Figure 3), are insulating tubes wrapped around the nerve with exposed inner contact points for stimulation and recording.

Interfascicular PNIs penetrate the epineurium but do not disrupt the blood-nerve barrier. Simulations have shown that electrodes positioned closer to the fascicles can preferentially activate nerve fibers within the fascicle while avoiding activation of other fibers in the nerve trunk. Due to the limited examples of interfascicular PNIs in the literature, it can be inferred that the main challenges in their design include the placement of electrodes between fascicles of irregular shapes and sizes, electrical isolation between fascicles, and the severity of the body's reaction during chronic use.

Fig. 3: Extraneural PNIs [2]

Despite the inevitable nerve damage, numerous studies have investigated the use of intrafascicular PNIs (Figure 4), which benefit from the insulating properties of the perineurium and can provide more efficient stimulation, sub-fascicular selectivity, a higher signal-to-noise ratio, and better signal detection compared to other PNIs. The primary challenge with intrafascicular PNIs lies in the risk of damaging nerve fibers and intraneural blood vessels, which can impair long-term functionality.

Fig. 4: Intrafascicular PNIs [2]

Regenerative PNIs (Figure 5) aim to leverage the well-known regenerative capability of peripheral nerves, which can reconnect after transection. Instead of implanting electrodes within the nerve, the nerve fibers regenerate and integrate with the electrodes inside the PNI. If successful, regenerative PNIs could potentially offer significantly higher resolution and stability compared to other types of PNIs discussed so far. A drawback is the need to transect the nerve, limiting use in applications requiring nerve integrity, like bioelectronic medicine. It is better suited for cases where distal innervation is non-essential, such as prosthetic limbs integration.[2].

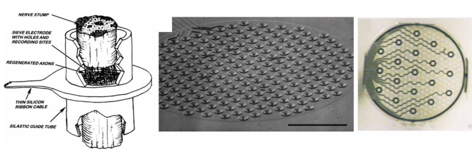

Fig. 5: Regenerative PNIs [2]

IV Hardware for Peripheral Nerve Interfaces

Challenges in Hardware Design for Neural Interfaces

An ideal peripheral nervous system interface should record biological signals robustly and consistently. State-of-the-art devices aim for low noise levels to preserve the signal-to-noise ratio despite neural signals' inherently small amplitudes. These devices must also achieve high spatial selectivity while minimizing potential harm to the biological environment. However, several challenges arise during the development of such interfaces, as outlined below. Low signal strength is a critical limitation, as neural signals in the PNS are typically minimal, ranging from 0.5 to 2 μV RMS [4]. These weak signals are susceptible to contamination from noise, particularly when long cables connect the electrodes to amplifiers, introducing significant interference that can obscure neural activity. Another significant challenge is the need for numerous cables, which increases tethering forces and can potentially cause physical damage to the tissue. Additionally, spatial constraints play a crucial role; these devices must be compact enough to fit within the limited space available while reducing the foreign body response in the biological system.

Solutions in Amplification and Signal Acquisition

Despite the persistent challenges in neural interface design, various solutions have been developed to enhance performance by combining noise reduction techniques with selective amplification. One notable advancement involves eliminating long cables, which significantly reduces noise contamination. However, achieving an optimal balance between current and voltage noise remains critical, necessitating careful bandwidth control and often requiring application-specific amplifiers. A key objective in optimizing the signal-to-noise ratio (SNR) is to achieve an ideal source resistance, defined as $R_{s(\text{optimum})} = \frac{e_n}{i_n}$, where e_n and i_n are the input voltage and current noise, respectively. Although $R_{s(\text{optimum})}$ is typically higher than the inherent source resistance of the system, introducing an additional resistor to bridge this gap often adds noise, which can counteract SNR optimization efforts. To address this, several innovative approaches have been proposed and successfully implemented. On-site amplification, which involves placing amplifiers close to the electrodes, significantly reduces noise caused by long transmission lines. Hardware averaging, another effective technique, connects each electrode to multiple identical devices operating in parallel, resulting in an effective source resistance of $R_{s(\text{optimum})} = \frac{e_n}{i_n \times N}$, where N is the number of devices[5][4]. Similarly, power matching uses transformers to increase the effective source resistance, with the relationship expressed as $R_{s(\text{optimum})} = \frac{e_n}{i_n \times n^2}$, where n is the transformer turns ratio. Together, these strategies offer promising solutions for mitigating noise and improving the fidelity of neural interface systems [4].

Drawbacks and Limitations

Modern amplifier and circuitry designs offer numerous advantages but are not without their limitations. A key concern is increased power consumption, particularly in systems that use parallel amplifiers, which experience a cumulative rise in energy demands. This issue is especially critical for electrodes used in long-term, chronic applications lasting several years. Rapid battery depletion in such cases necessitates either battery replacement surgeries or the integration of rechargeable batteries. Scalability is another significant challenge. Techniques like hardware averaging and transformer-based power matching become increasingly complex as the system grows. Power matching, for example, often requires large transformers, which limit the number of channels that can be implemented within a given space. Despite the proposed solutions significantly enhancing signal quality, noise remains a major limitation. Power matching would still suffer from insufficient sources for optimizing their transformers' turn ratio. Similarly, hardware averaging inherently suffers from a cumulative increase in input current noise.

Hardware Systems

Many available devices have been demonstrated to find a reasonable balance between these constraints [6]. To reiterate what has been explained before, these devices can be categorized into two main groups based on their invasiveness. Extraneural electrodes, such as cuff and FINE electrodes, do not penetrate the nerve but merely surround it. While both are relatively considered non-invasive, one could argue that the FINE electrode, which compresses the circular nerve into a rectangular shape, achieves better signal measurement at the cost of being more invasive, as excessive compression might damage the nerve. Similarly, there are invasive electrodes that perturb the nerve. Examples include the TIME and LIFE electrodes, both of which penetrate the nerve. The TIME electrode traverses the nerve transversely, while the LIFE electrode traverses it longitudinally. The various electrodes are illustrated in Figure 6.

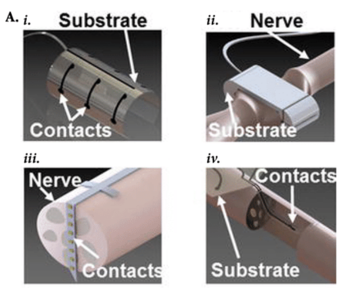

Fig. 6: Various peripheral nerve interfaces are diagrammed. Extraneural interfaces such as i. cuff electrodes and ii. flat interface nerve electrodes (FINE) surround the nerve. Intraneural interfaces such as iii. transverse intrafascicular multichannel electrodes (TIME) and iv. longitudinal intrafascicular electrodes (LIFE) penetrate the nerve

One notable example of a complete advanced hardware system is the FINE cuff electrode with on-cuff electronics, combined with the circuitry presented below. This system integrates a 16-channel low-noise amplifier, achieving a noise level of 0.78 μV RMS for the frequency range of 700 Hz to 5 kHz by incorporating the hardware averaging technique with $N = 4$, along with multiplexers and digitizers. The design offers several advantages, including a compact form factor, a high signal-to-noise ratio (SNR), and reduced tethering forces. Another benefit of this circuit is its scalability, allowing for duplication by placing one on each side, thereby increasing the number of channels to 32 while still maintaining the same noise performance as well as on device processing.

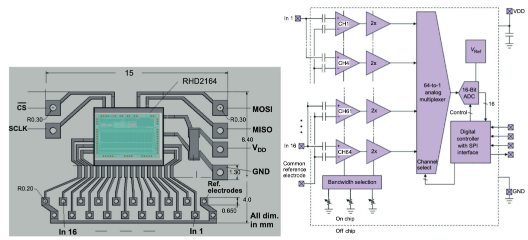

Fig. 7: Left: Circuit layout for on-cuff electronics. This system is capable of recording 16 channels of ENG at 15 kHz each with $< 1\mu V_{RMS}$ inputreferred noise and will fit on the back of a typical FINE. One of these circuits may be placed on each side for 32 channel recordings. A multiplexer and analog-to-digital converter are included in the package, reducing the number of wires and hence the force on the cuff, from 20 to 6. Right: Modified schematic of the Intan RHD2164 chip with the external connection of four parallel devices per electrode contact to implement hardware averaging for noise reduction.

V Data Processing

Lower limb EMG decoding

The movement of powered lower-limb prosthesis depends on the ability to decode in real time motor intentions from non-invasive electrode signals like electromyograms. In a recent study[7], EMG electrodes were placed on the residual muscles of 13 subjects, and the electrical activity from these muscles was recorded alongside motion data detecting gait events like heel and toe strikes. This aimed to predict the user's intended movements during various tasks such as level-ground walking, stair navigation, and ramp ascent/descent. This data is input into a support vector machine (SVM) classifier, which was trained to classify motor tasks based on the extracted features. The algorithm focused on decoding motor intentions early in the gait cycle, leveraging sliding observation windows to enhance computational efficiency. The optimal setup, combining data from three EMG channels and IMUs, achieved a decoding accuracy of over 94% while maintaining minimal computational complexity, particularly when using a linear SVM.

Wavelet denoising and spike sorting for electroneurographic signal processing

Invasive approaches of PNS interfaces for prosthesis control rely heavily on the ability to differentiate efferent signals from afferent ones. To that end, two main methods are combined in literature[8], wavelet denoising and spike sorting.

Wavelet denoising is a robust method to reduce noise while preserving the critical features of the neural signal. The process involves transforming the raw ENG data into an orthogonal time-frequency domain using a translation-invariant wavelet transform, which decomposes it into coefficients representing different frequency components. Noise components, assumed to follow a Gaussian distribution, are filtered by applying a threshold to the wavelet coefficients before reconstructing the signal. This ensures that transient neural features, like spikes, are retained while minimizing background noise.

Following denoising, spike sorting is applied to identify and classify individual spike waveforms. The process begins by detecting spikes that exceed a predefined threshold, segmenting their waveforms into fixed windows and clustering them into distinct groups using machine learning or statistical methods. These clusters correspond to different neurons, enabling researchers to study neural activity at a single-unit level.

VI Clinical Applications

Peripheral nerve stimulation for pain relief

Today, peripheral nerve stimulation can be used for pain relief in patients suffering from chronic pain disorders which have been failed by other types of treatment like medications and physical therapy.

One example of that is the treatment of trigeminal neuralgia, which is a condition of neuropathic facial pain. It can be caused by compression of the root nerve and complications from other neurological conditions such as multiple sclerosis, or, like a lot of other chronic pain disorders, it can have no discernable causes[9]. PNS is emerging as a promising treatment for this condition.

A study analyzing case series of trigeminal neuralgia patients treated with PNS shows a typical process for these trials[10]. Nineteen patients first underwent percutaneous trial stimulations before permanent implantation. Different regions of the face depending on pain location and different stimulation parameters were tested, only subjects demonstrating significant pain relief were considered for permanent implantation. Electrodes are implanted on the relevant trigeminal branches and stimulation is left under the control of the patient with appropriate thresholds of intensity. Long term follow-ups (6 to 58 months) showed that patients still receiving stimulation reported a mean pain reduction of 52.3% .

This is one of many studies showing promising results regarding the efficacy of this treatment[11], however research in this field has its limitations. In the aforementioned study, 20% of patients experienced infections, and overall, studies on PNS for trigeminal neuralgia show higher incidences of complications than other stimulation methods such as spinal chord stimulation[12]. Efficacy of pain relief seems to be dependent on the stimulation target and etiology of trigeminal neuralgia.[11]. Further research and randomized controlled trials are warranted before PNS of the trigeminal nerve can be considered as a common clinical treatment of trigeminal neuralgia.

Peripheral nerve recording for prosthesis control

Restoration of sensory-motor function in patients having lost a limb due to disease, injury or amputation is a crucial field of research that could improve the lives of millions. There are currently many research groups developing neurocontrolled prosthesis using different approaches. One of which is based on the recording of efferent nervous signals in the nerves and muscles of the residual limb for prothesis control and stimulation of afferent nerves for sensory feedback.

Invasive electrodes, such as intrafascicular and regenerative electrodes, provide high-resolution signal acquisition and bidirectional communication. Intrafascicular electrodes, for example longitudinal intrafascicular electrodes (LIFEs), are inserted along the length of a nerve, positioned between and parallel to nerve fibers. They have demonstrated the ability to distinguish signals originating from different areas of the skin and accurately decode motor intentions[13][14]. Additionally, intrafascicular electrodes can deliver sensory feedback by stimulating specific nerve fibers, enabling users to feel sensations such as pressure or touch from their prosthetic limbs[13]. Despite their promising capabilities, they are limited by a restricted number of recording channels and long-term biocompatibility concerns for their widespread clinical application consideration. In contrast, regenerative electrodes, or sieve electrodes, rely on axonal regeneration, where nerve fibers grow through micro-scale holes in the electrode array, establishing direct contact with individual axons or small groups. This design allows for an interface with a potentially larger number of axons and higher SNR than other electrode types[15][16]. However, their functionality depends on the quality and consistency of axon regeneration, which can be unpredictable and time-consuming.

A recent case study proposes a new design for a soft transfemoral prosthetic socket[17] for lower limb amputees which would allow integration of sensors on the residual limb skin interface. EMG sensors decode the user's movement intentions, achieving a median accuracy of 73% in motor intention classification during various walking tasks, while vibrotactile units provide sensory feedback to enhance user interaction and balance. Accuracy could be further enhanced with techniques such as muscle reinnervation[18], however it requires surgical intervention. Additionally, the temperature and humidity sensors monitor the thermal conditions of the residual limb, permitting better health monitoring. The ability to decode user intent accurately and provide real-time sensory feedback not only enhances prosthetic control but also promotes a better gait recovery.

VII Conclusion

Peripheral nerve interfaces have the potential to revolutionize medicine and human-machine interaction. In the future, further miniaturization and biocompatibility improvements will enhance the longevity and integration of PNIs with the human body. Advances in signal processing, including the incorporation of artificial intelligence and machine learning, will refine our ability to decode complex neural signals, leading to more precise and naturalistic control of prosthetics and other devices. Hybrid approaches that combine invasive and non-invasive techniques could overcome the gap between performance and usability, thus broadening their clinical impact. Beyond restoring lost functions, in the future, PNIs may also be able to easily integrate with brain-computer interfaces and provide targeted treatments of neurological disorders.

References

[1] Sanghoon Lee and Chengkuo Lee. "Toward advanced neural interfaces for the peripheral nervous system (PNS) and their future applications". In: *Current opinion in biomedical engineering* 6 (2018), pp. 130–137.

[2] Christopher E Larson and Ellis Meng. "A review for the peripheral nerve interface designer". In: *Journal of neuroscience methods* 332 (2020), p. 108523.

[3] Valentina Paggi et al. "Compliant peripheral nerve interfaces". In: *Journal of neural engineering* 18.3 (2021), p. 031001.

[4] B. Wodlinger, Y. Dweiri, and D. M. Durand. "Biochips". In: *Implantable Biomedical Microsystems* (2015), pp. 203–214. DOI: 10.1016/B978-0-323-26208-8.00009-1.

[5] Yazan M. Dweiri et al. "Ultra-low noise miniaturized neural amplifier with hardware averaging". In: *Journal of Neural Engineering* 12.4 (2015), p. 046024. DOI: 10.1088/1741-2560/12/4/046024.

[6] M. M. Iskarous and N. V. Thakor. "E-Skins: Biomimetic Sensing and Encoding for Upper Limb Prostheses". In: *Proceedings of the IEEE* 107.10 (Oct. 2019), pp. 2052–2064. DOI: 10.1109/JPROC.2019.2939369.

[7] Federica Barberi et al. "Early decoding of walking tasks with minimal set of EMG channels". en. In: *J. Neural Eng.* 20.2 (Apr. 2023), p. 026038. ISSN: 1741-2560, 1741-2552. DOI: 10.1088/1741-2552/acc901. URL: https://iopscience.iop.org/article/10.1088/1741-2552/acc901 (visited on 12/02/2024).

[8] Luca Citi et al. "On the use of wavelet denoising and spike sorting techniques to process electroneurographic signals recorded using intraneural electrodes". en. In: *Journal of Neuroscience Methods* 172.2 (July 2008), pp. 294–302. ISSN: 01650270. DOI: 10.1016/j.jneumeth.2008.04.025. URL: https://linkinghub.elsevier.com/retrieve/pii/S0165027008002586 (visited on 12/02/2024).

[9] Giorgio Cruccu et al. "Trigeminal neuralgia: New classification and diagnostic grading for practice and research". en. In: *Neurology* 87.2 (July 2016), pp. 220–228. ISSN: 0028-3878, 1526-632X. DOI: 10.1212/WNL.0000000000002840. URL: https://www.neurology.org/doi/10.1212/WNL.0000000000002840 (visited on 12/02/2024).

[10] Robert W. Bina et al. "Peripheral Nerve Stimulation for Refractory Trigeminal Pain: Recent Single-Institution Case Series With Long-Term Follow-Up and Review of the Literature". en. In: *Neuromodulation: Technology at the Neural Interface* 23.6 (Aug. 2020), pp. 796–804. ISSN: 10947159. DOI: 10.1111/ner.13132. URL: https://linkinghub.elsevier.com/retrieve/pii/S1094715921002488 (visited on 12/02/2024).

[11] Yuncheng Ni et al. "Implantable Peripheral Nerve Stimulation for Trigeminal Neuropathic Pain: A Systematic Review and Meta-Analysis". en. In: *Neuromodulation: Technology at the Neural Interface* 24.6 (Aug. 2021), pp. 983–991. ISSN: 10947159. DOI: 10.1111/ner.13421. URL: https://linkinghub.elsevier.com/retrieve/pii/S1094715921062310 (visited on 12/02/2024).

[12] Zhangyan Mao et al. "Peripheral Nerve Stimulation for Neuropathic Pain Management: A Narrative Review". en. In: *Pain Ther* 13.6 (Dec. 2024), pp. 1387–1406. ISSN: 2193-8237, 2193-651X. DOI: 10.1007/s40122-024-00659-6. URL: https://link.springer.com/10.1007/s40122-024-00659-6 (visited on 12/02/2024).

[13] S. Micera et al. "Decoding Information From Neural Signals Recorded Using Intraneural Electrodes: Toward the Development of a Neurocontrolled Hand Prosthesis". en. In: *Proc. IEEE* 98.3 (Mar. 2010), pp. 407–417. ISSN: 0018-9219, 1558-2256. DOI: 10.1109/JPROC.2009.2038726. URL: http://ieeexplore.ieee.org/document/5415651/ (visited on 12/02/2024).

[14] Paolo M. Rossini et al. "Double nerve intraneural interface implant on a human amputee for robotic hand control". en. In: *Clinical Neurophysiology* 121.5 (May 2010), pp. 777–783. ISSN: 13882457. DOI: 10.1016/j.clinph.2010.01.001. URL: https://linkinghub.elsevier.com/retrieve/pii/S1388245710000039 (visited on 12/03/2024).

[15] Xavier Navarro et al. "A critical review of interfaces with the peripheral nervous system for the control of neuroprostheses and hybrid bionic systems". en. In: *J Peripheral Nervous Sys* 10.3 (Sept. 2005), pp. 229–258. ISSN: 1085-9489, 1529-8027. DOI: 10.1111/j.1085-9489.2005.10303.x. URL: https://onlinelibrary.wiley.com/doi/10.1111/j.1085-9489.2005.10303.x (visited on 12/02/2024).

[16] Philip P Vu et al. "Long-term upper-extremity prosthetic control using regenerative peripheral nerve interfaces and implanted EMG electrodes". en. In: *J. Neural Eng.* 20.2 (Apr. 2023), p. 026039. ISSN: 1741-2560, 1741-2552. DOI: 10.1088/1741-2552/accb0c. URL: https://iopscience.iop.org/article/10.1088/1741-2552/accb0c (visited on 12/03/2024).

[17] Linda Paternò et al. "Soft Transfemoral Prosthetic Socket With Sensing and Augmenting Feedback: A Case Study". en. In: *IEEE Trans. Med. Robot. Bionics* 6.2 (May 2024), pp. 536–547. ISSN: 2576-3202. DOI: 10.1109/TMRB.2024.3381378. URL: https://ieeexplore.ieee.org/document/10480738/ (visited on 12/02/2024).

[18] Todd A Kuiken et al. "Targeted reinnervation for enhanced prosthetic arm function in a woman with a proximal amputation: a case study". en. In: *The Lancet* 369.9559 (Feb. 2007), pp. 371–380. ISSN: 01406736. DOI: 10.1016/S0140-6736(07)60193-7. URL: https://linkinghub.elsevier.com/retrieve/pii/S0140673607601937 (visited on 12/02/2024).