Peripheral Nerve Interfaces

Topic 4

Evan Massonnet
evan.massonnet@epfl.ch

Daniel Bach
daniel.bach@epfl.ch

***Abstract*—Peripheral nerve interfaces (PNIs) have emerged as a critical technology for restoring motor function, sensory perception, and bidirectional communication between humans and advanced prosthetic or neurorehabilitation systems. Over the past decades, significant progress has been made in both invasive and non-invasive approaches, ranging from surface electrodes and cuff electrodes to intraneural devices such as longitudinal intrafascicular electrodes (LIFEs), transverse intrafascicular multichannel electrodes (TIMEs), and targeted muscle reinnervation. These technologies aim to achieve stable, selective, and long-term interfacing with peripheral nerves despite biological and mechanical challenges such as signal degradation, fibrotic encapsulation, and electrode–tissue impedance changes. This paper reviews the state of the art in peripheral nerve interfaces.**

I. INTRODUCTION

Although the central nervous system (CNS) performs the majority of the information storage and processing tasks that interest neuroscientists, reliably interfacing with these signals remains technically challenging. By contrast, the peripheral nervous system (PNS) is primarily devoted to transmitting information, and its signals often contain rich and clinically valuable content. For instance, lower motor neurons convey muscle activation commands that do not require the complex decoding associated with cortical signals, offering a significant advantage for prosthetic control. Peripheral nerves also serve as conduits between the body's biological sensors and their regulatory mechanisms. A well-designed neural interface could therefore enable continuous monitoring of diverse physiological variables, such as blood glucose levels, blood pressure, or sensory inputs, while simultaneously supporting or augmenting compromised biological control systems.

Peripheral nerve electrodes are commonly categorized by their level of invasiveness, particularly by whether they penetrate neuronal membranes. Extraneural devices such as oval or spiral cuff electrodes encircle the nerve without entering its internal structure. Other technologies, including the Utah Electrode Array and longitudinal intrafascicular electrodes (LIFEs), penetrate both the epineurium and the perineurium. Because penetrating electrodes position recording sites in close proximity to the axons, they can achieve substantially higher signal-to-noise ratios (SNRs), although long-term stability remains an unresolved challenge [1].

II. PERIPHERAL NERVE SYSTEM: ANATOMY AND PHYSIOLOGY

The peripheral nervous system (PNS), is the part of the nervous system that lies outside the brain and spinal cord. It is an extensive communication network that ensures the brain and spinal cord can interact with every organ, muscle, and sensory surface of the body. Unlike the brain and spinal cord, which are protected by bone, the PNS is exposed throughout the body, making it more vulnerable to injury but also more flexible in structure and function.

Functionally, the PNS is divided into two major parts. The somatic nervous system manages voluntary actions and conscious sensations. The second part, the autonomic nervous system, regulates processes that operate without conscious effort, such as heart rhythm, blood pressure, digestion, pupil dilation, and respiratory rate. This system has two complementary divisions: the sympathetic system, which prepares the body for action by increasing heart rate and mobilizing energy, and the parasympathetic system, which restores balance by slowing the heart, promoting digestion, and supporting recovery. These systems work together continuously to maintain internal stability despite changing external conditions. [1], [2]

III. APPLICATIONS OF PERIPHERAL NERVE INTERFACES

A. *Intuitive Prosthetic Control via Bio-Hybrid Systems*

The most mature application of PNIs is in restoring motor function for individuals with limb loss. The key advancement has been the shift to bio-hybrid interfaces, which utilize the regenerative capacity of the peripheral nervous system (PNS) to naturally amplify neural signals. Techniques like Targeted Muscle Reinnervation (TMR) or Regenerative Peripheral Nerve Interfaces (RPNIs) redirect residual efferent nerve fibers into denervated or free-grafted muscle, respectively [3]. These reinnervated muscles function as biological amplifiers, converting low-amplitude μV nerve action potentials into robust mV-scale compound muscle action potentials that are easily recorded by implanted intramuscular electrodes.

This bio-amplification is crucial because it provides stable, spatially separated myoelectric signals that are a direct representation of the user's original motor intent, overcoming the issue of electromyographic (EMG) crosstalk inherent to surface recordings. For high-degree-of-freedom prostheses, even greater precision is achieved using penetrating electrodes, such as Transverse/Longitudinal Intrafascicular Electrodes (T/LIFEs). These devices access the nerve's internal structure, enabling fascicular selectivity—the ability to record or stimulate specific bundles of axons corresponding to individual movements, such as a finger or a wrist flexion. This granular control is unattainable with non-invasive methods, making it the foundational technology for true dextrous prosthetic manipulation.

B. Somatotopic Sensory Feedback and Reduced Cognitive Load

The capacity for bidirectional communication is a decisive PNI advantage, particularly in sensory restoration. Unlike the CNS, the PNS is organized somatotopically, meaning that stimulation of a specific afferent fascicle results in a sensation perceived precisely at the phantom limb location (e.g., a touch felt on the phantom index finger). This biomimetic feedback is delivered through current-controlled stimulation of afferent fibers, effectively closing the sensorimotor loop [].

The functional benefit of this naturalistic feedback is a dramatic reduction in the user's cognitive load. In real-world, dual-task paradigms (e.g., using a prosthesis while performing a simultaneous mental task), subjects relying on artificial PNI sensation exhibit performance and manual accuracy that is significantly more robust than those relying solely on visual feedback or non-invasive sensory aids (like vibrating motors). This phenomenon suggests that the brain processes the neurally delivered sensation at a low, pre-conscious level, analogous to natural reflexes, thereby liberating cognitive resources for higher-level planning. The PNI is thus superior not only for signal quality but also for the overall efficiency and embodiment of the prosthetic device.

C. Targeted Neuromodulation for Pain and Autonomic Disorders

Beyond replacing lost function, PNIs are increasingly used in bioelectronic medicine for therapeutic neuromodulation, offering a minimally invasive alternative to central nervous system interventions. The PNS provides direct access to specific regulatory pathways, which is critical for systemic diseases [3].

A prime example is Vagus Nerve Stimulation (VNS). The vagus nerve (Cranial Nerve X) is the main component of the parasympathetic system, and its afferent fibers provide a gateway to modulate the inflammatory reflex via the splenic nerve. Chronic VNS is an FDA-approved treatment for refractory epilepsy and depression, but cutting-edge research is applying it to suppress systemic inflammation in conditions like rheumatoid arthritis and Crohn's disease [4].

Similarly, in pain management, electrodes targeting peripheral nerves—such as the occipital nerves for chronic migraines or the dorsal root ganglia (DRG) for focal neuropathic pain—offer highly selective control. In contrast to traditional spinal cord stimulation, which recruits large regions of the spinal cord, DRG stimulation allows for the targeted modulation of small populations of primary sensory neurons, providing superior pain coverage with lower power consumption. These applications capitalize on the organizational specificity of the PNS to effect precise, localized change in physiological state without systemic side effects [5].

IV. CLASSIFICATION OF PERIPHERAL NERVE INTERFACES

Peripheral nerve interfaces can be categorized according to their level of invasiveness and the manner in which they interact with the internal structure of the nerve. Each class of device represents a different compromise between selectivity, long-term stability, biological risk, and signal quality. The following sections present the main classes of peripheral nerve electrodes, the technical challenges they address, the solutions they implement, and their respective advantages and limitations. [6]

A. Cuff-Style Electrodes

Cuff electrodes represent the least invasive category of peripheral nerve interfaces. They wrap around the external surface of the nerve without penetrating the epineurium, which makes them mechanically stable and generally safe for chronic implantation. Their central challenge is achieving meaningful neural recordings or stimulation while remaining outside the nerve, where signals are weak and fascicular selectivity is limited. [1], [7]

Cylindrical cuffs fully encircle the nerve in a closed loop. They are typically constructed from flexible, biocompatible materials such as silicone, into which metal contacts are embedded. By surrounding the nerve, cylindrical cuffs ensure consistent electrode–tissue contact and reduce susceptibility to displacement caused by limb motion. Their main advantage is their excellent long-term biocompatibility: because they do not penetrate neural membranes, they provoke minimal inflammation or fibrotic encapsulation. This stability makes them well suited for chronic stimulation applications, such as vagus nerve stimulation or functional electrical stimulation. However, electrically, they can only access the sum of activity from all fascicles within the nerve, resulting in low selectivity. The distance between axons and electrode contacts also leads to low-amplitude signals.

Flat Interface Nerve Electrodes (FINE) attempt to increase selectivity while maintaining the non-penetrating nature of cuff electrodes. They reshape the nerve from a cylindrical cross-section into a flatter geometry, bringing individual fascicles closer to the electrode contacts.The benefit of the FINE design lies in its improved access to the spatial organization of the nerve. By reducing the average distance between electrodes and fascicles, FINE can achieve more selective stimulation and better recording quality without the invasiveness of intraneural devices. However, the imposed reshaping can introduce mild mechanical stress on the nerve, and the selectivity improvements, while significant compared with cylindrical cuffs, still do not match that of penetrating electrodes. Additionally, long-term reshaping may alter nerve physiology in unpredictable ways [2], [6].

B. Penetrating Electrodes

Penetrating electrodes are designed to overcome the limitations of extraneural devices by bringing the recording and stimulation sites directly into the interior of the nerve fascicles. This dramatically improves selectivity and signal-to-noise ratio but introduces biological and mechanical challenges.

The Utah Slanted Electrode Array (USEA) is a three-dimensional array of microneedles, each penetrating the nerve to a controlled depth. Its slanted configuration allows electrodes at different lengths to target different fascicles within the same nerve cross-section. However, insertion requires careful surgical technique, and the rigid structure of the array creates mechanical mismatch with soft neural tissue. This mismatch leads to micromotion damage, chronic inflammation, and eventual signal degradation, limiting long-term reliability.

The Transverse Intrafascicular Multichannel Electrode (TIME) is designed to traverse the nerve transversely, passing through one or more fascicles. By placing a series of electrode sites along a flexible transverse shank, the TIME directly addresses the need for selective access to multiple fascicles The flexibility of the device reduces mechanical mismatch and improves biocompatibility. While more stable than rigid intraneural arrays, it may still suffer from inflammatory encapsulation or shifts in electrode position due to tissue regeneration or movement.

Longitudinal Intra-Fascicular Electrode (LIFE) are thin, flexible wires inserted along the length of a fascicle, placing them in intimate contact with axons that run parallel to the electrode. This orientation solves the challenge of achieving stable recordings by aligning the electrode with the natural direction of action potential propagation. Their main advantage is that they provide high-quality, selective recordings with minimal disruption to the fascicular structure compared with transverse devices. Drawbacks include the invasiveness of penetrating the perineurium and the risk of long-term drift or misalignment due to tissue movement [2], [7].

C. Sieve Electrodes

Sieve or regeneration-style electrodes incorporate microscopic holes through which regenerating axons grow after nerve transection. By forcing axons to pass through predefined channels that contain embedded electrode sites, sieve technologies can achieve very high spatial resolution and selective access to specific groups of axons.

The main advantage of sieve electrodes is their potential for single-axon or small-fascicle resolution, enabling levels of selectivity far beyond what traditional cuff or penetrating electrodes can offer. Because axons grow directly through the device, the electrode–axon interface can be exceptionally close and stable. This approach requires nerve transection and regeneration, which is a major surgical intervention with uncertain functional outcomes. Axonal regrowth is slow, unpredictable, and may not reconstruct natural fascicular organization, potentially compromising signal quality or nerve function. These drawbacks limit the clinical applicability of sieve electrodes despite their high theoretical selectivity. [8]

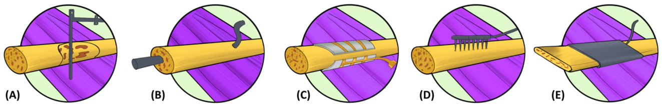

Fig. 1. (A) Transverse intrafascicular multichannel electrode—TIME; (B) longitudinal intra-fascicular electrode—LIFE; (C) Cuff; (D) Utah Slanted Electrode Array—USEA; and (E) flat interface nerve electrode—FINE. [2]

V. SIGNAL ACQUISITION, PROCESSING, AND DECODING

A. Signal Acquisition: Interfacial Impedance and Chronic Stability Modeling

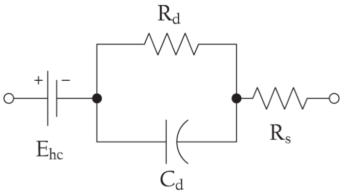

Fig. 2. Electrode electrical model

The design of a chronic PNI is fundamentally constrained by the physics of the electrode-tissue interface, which is modeled as a complex equivalent circuit. This circuit typically includes the double-layer capacitance (C_{dl}), charge transfer resistance (R_{ct}), and the spreading resistance of the tissue (R_s). For high-fidelity recording, engineers seek high C_{dl} (which favors small electrodes) and low overall impedance in the frequency band of interest (typically $300Hz$ to $7kHz$ for neural spikes).

The Stability-Fidelity Trade-Off This quest for high fidelity inherently clashes with biological stability. Penetrating microelectrodes (e.g., T/LIFEs) initially offer the lowest R_s and highest Signal-to-Noise Ratio (SNR) by placing contacts near the axons. However, the subsequent foreign body response results in a progressive layer of glial encapsulation. This biological layer acts as a dielectric material, causing a chronic, exponential increase in impedance—modeled as an increase in R_{ct} and a decrease in C_{dl} — which degrades the electrode's transfer function and leads to significant signal non-stationarity and unit loss over time. This makes the system unreliable for chronic use without frequent recalibration.

Bio-Hybrid Impedance Management The bio-hybrid interface (e.g., Regenerative Peripheral Nerve Interface (RPNI)) provides an elegant engineering solution by sidestepping the intraneural impedance problem entirely. By routing the residual nerve to reinnervate a muscle, the system exploits the biological gain of the neuromuscular junction. The muscle acts as a stable, low-noise, high-gain physiological amplifier, converting the weak neural signal into a robust, mV-scale Compound Muscle Action Potential (CMAP). The recording electrodes are then placed in the stable, low-impedance muscle matrix. This shift simplifies the front-end amplifier design in the implantable pulse generator (IPG), reducing the required gain, minimizing noise contribution from the electronics, and drastically improving the long-term reliability metric of the interface.

B. Signal Processing: Real-Time Filtering and Dimensionality Expansion

The central constraint during signal processing is satisfying the real-time control latency budget—a hard limit typically set below $100ms$ for seamless user interaction—while executing computationally intensive noise reduction and feature extraction algorithms. This mandates highly optimized, low-power implementations, often utilizing ASICs or FPGAs for parallel processing [9].

Adaptive Filtering and Latency Minimization Raw signals are contaminated by various noise sources, requiring sophisticated filtering. The neural spike data is often bandpass filtered (e.g., $300Hz$ to $7kHz$) using high-order Butterworth or Chebyshev filters to isolate action potentials. A key challenge is managing the group delay introduced by these filters, which is the time delay experienced by different frequency components. Non-linear phase response can lead to signal distortion and push the system beyond the strict latency threshold. To combat real-world, time-variant noise (e.g., power-line interference, movement artifact), adaptive digital filtering techniques, such as Wiener filtering or Least Mean Squares (LMS) algorithms, are necessary. These algorithms continuously estimate and subtract the noise component, requiring significant on-board computation but providing crucial noise robustness.

Dimensionality Expansion via MUAP Sorting For penetrating arrays, the number of independent physical electrode contacts is insufficient to map the full kinematics of the amputated limb. To overcome this channel bandwidth limitation, the system performs Motor Unit Action Potential (MUAP) sorting. This process is a complex pattern recognition task:

1) Spike Detection: Thresholding or nonlinear energy operators are used to isolate individual spikes.
2) Feature Extraction: Waveform features (e.g., maximum and minimum amplitude, Principal Component Analysis (PCA) coefficients) are extracted.
3) Clustering: Unsupervised learning algorithms (K-means or Gaussian Mixture Models) cluster these features to uniquely identify the source—an individual Motor Unit (MU).

By tracking the instantaneous firing rate of each classified MU, the system creates multiple ”virtual channels” from a single physical input, effectively expanding the dimensionality of the control signal. The primary engineering drawback is the fragility of the clustering: minute changes in spike shape due to electrode micromotion cause sorting errors (e.g., unit splitting or merging), manifesting as non-Gaussian noise in the feature vector [10].

C. Decoding: Dynamic State Estimation and Adaptive Control

The decoding stage is a dynamic systems problem: translating the processed, non-linear feature vector into a continuous, smooth, proportional kinematic output (e.g., position, velocity). This is primarily addressed using state estimation models [11].

State-Space Modeling for Continuous Control Static classifiers (like LDA) are limited to discrete movement classification and cannot achieve the smooth control required for natural manipulation. The preferred solution is the Kalman filter, a recursive estimator operating in a state-space representation. It models the system dynamics using a prediction step (based on the previous state and known dynamics) and an update step (which optimally fuses the prediction with the current noisy neural measurement). The Kalman filter provides an optimal minimum mean square error (MMSE) estimate of the prosthetic’s current state, making it highly robust against the inherent noise and uncertainty of biological signals while remaining computationally efficient for embedded hardware [12].

For highly non-linear dynamics and systems requiring temporal context (e.g., velocity integration), Recurrent Neural Networks (RNNs)—specifically LSTMs (Long Short-Term Memory) or GRUs (Gated Recurrent Units)—are being investigated. These models excel at learning the complex, non-linear, and temporal dependencies between past neural activity and current movement. However, their vast parameter space and matrix operation requirements pose a substantial challenge for power dissipation and on-chip memory footprint, making their chronic, high-speed, implantable implementation a leading focus of current neural hardware research.

Model Drift Compensation Chronic PNI functionality is ultimately limited by model drift. To maintain high decoding accuracy over the long term, online adaptive decoding algorithms are necessary. These algorithms employ recursive optimization techniques, such as Recursive Least Squares (RLS), which continuously update the model weights using a calculated error signal (the difference between the decoded output and the desired outcome, often provided by the user’s visual perception or artificial sensory feedback). The engineering challenge is the delicate calibration of the RLS forgetting factor: a value too close to zero causes the model to adapt too slowly, failing to track chronic biological changes, while a value too close to one makes the model overly sensitive to instantaneous noise, leading to output instability and erratic prosthetic behavior. The chronic fidelity of the PNI system relies on this precisely tuned adaptive control loop.

VI. CONCLUSION

Peripheral nerve interfaces have become a key technology for restoring motor and sensory function, enabling intuitive prosthetic control, and advancing neuromodulation therapies. Their diversity reflects ongoing efforts to balance safety, selectivity, and long-term stability. While cuff electrodes offer reliable chronic performance with minimal tissue disruption, penetrating and regenerative interfaces provide superior signal quality at the cost of increased invasiveness and potential foreign-body responses. Continued integration of flexible materials, high-resolution fabrication, and refined signal processing is expected to drive the next generation of clinically effective and scalable peripheral neurotechnologies.

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