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Previews

Soft electrochemical actuators for intraoperative nerve activity monitoring

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Recent advances in nerve cuff electrodes, which integrate soft electrochemical actuators and neural microelectrodes, offer a minimally invasive method for peripheral nerve interfacing. Utilizing low-voltage electric actuation, these cuffs encircle peripheral nerves *in vivo*, providing adaptability for chronic and precise nerve monitoring and modulation.

The monitoring and modulation of peripheral nerve interfaces have emerged as indispensable tools in diagnosing and treating neurological disorders, providing innovative therapies for managing chronic pain and motor dysfunction.[1–3] Conventional approaches to peripheral nerve interfacing typically involve invasive surgical procedures for electrode implantation, posing significant risks of nerve damage and subsequent loss of function. Additionally, the rigidity of early electrode designs severely impacted the mechanical compatibility of the device and the soft tissue of peripheral nerves, often leading to scarring and impaired device performance over time.[4]

To address these issues, historical efforts in peripheral neural interfacing have focused on crafting devices that are not only soft and biocompatible[5] but also exhibit natural, long-term adhesion to nerve tissues.[6] Despite recent advancements, optimizing the multilayered structures of these devices for compact integration continues to present challenges in ensuring flexibility, adhesion, and sustained signal fidelity for effective and adaptive peripheral neural interfacing.

A recent study published in *Nature Materials* introduces a hybrid cuff actuating electrode, integrating electrically driven, conducting-polymer-based soft actuators and neural microelectrodes.[7] This innovation enhances the adaptability of nerve interfaces by allowing the electrodes to gently grasp and encircle peripheral nerves at a low voltage range of 0.4–0.6 V. Careful consideration of the mechanical properties and geometry of the actuatable nerve cuff design is essential for achieving a conformal fit across various peripheral nerve sizes, spanning from several hundred micrometers to a few millimeters in diameter. This ensures effective signal transmission and stimulation while minimizing invasiveness and the risk of nerve damage. The high-resolution microfabrication of this soft actuating microelectrode entails several steps: photolithography using AZ 5214E positive photoresist for patterning, chemical vapor deposition (CVD) of parylene C (PaC) for substrate and insulation layers, and electrochemical deposition of polypyrrole (PPy) doped with dodecylbenzene sulfonate (DBS) (Figure 1A). PaC is favored due to its exceptional biocompatibility, chemical inertness, and superior barrier properties, making it an ideal choice for both the substrate and encapsulation layers in cuff electrodes. It surpasses alternatives such as SU-8, which is too rigid for flexible cuff nerve interfaces, and PDMS, whose permeability to gases and moisture could compromise the insulation properties and integrity of the device during long-term implantation. Furthermore, doping PPy with DBS enhances its ionic conductivity and stability in biological environments, facilitating the reversible expansion and contraction induced by ion transport for low-voltage actuation. Conductive poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS), although commonly utilized as a neural electrode material, lacks the necessary mechanical properties for active nerve cuff actuation. Therefore, PEDOT:PSS is integrated with actuators to capture electrical signals from peripheral nerves and administer electrical stimulation (Figure 1B), achieving low impedance while maintaining this characteristic even after 1,000 bending cycles (Figure 1C). Upon application of voltage, the PPy/Au actuators curl to envelop the nerve (Figures 1D and 1E), dynamically adapting their shape to precisely position the electrodes against the neural tissue. This ensures high-fidelity data acquisition and direct stimulation at the neural interface, mitigating complications such as misalignment and signal attenuation. The pronounced changes in curvature (α) and corresponding spikes in DBS, compared to phosphate-buffered saline (PBS), indicate that DBS enhances actuation dynamics and electrode responsiveness (Figure 1F). The temporal correlation observed between the "Press" event and the spike (Figure 1G) showcases the electrode's sensitivity and specificity in capturing nerve activity related to external stimuli. This underscores its potential utility in real-time intraoperative monitoring and postoperative recovery, facilitating precise nerve healing and restoration of function.[4] Subsequent endurance tests demonstrate the durability and robustness of the actuator across multiple cycles (Figure 1H).

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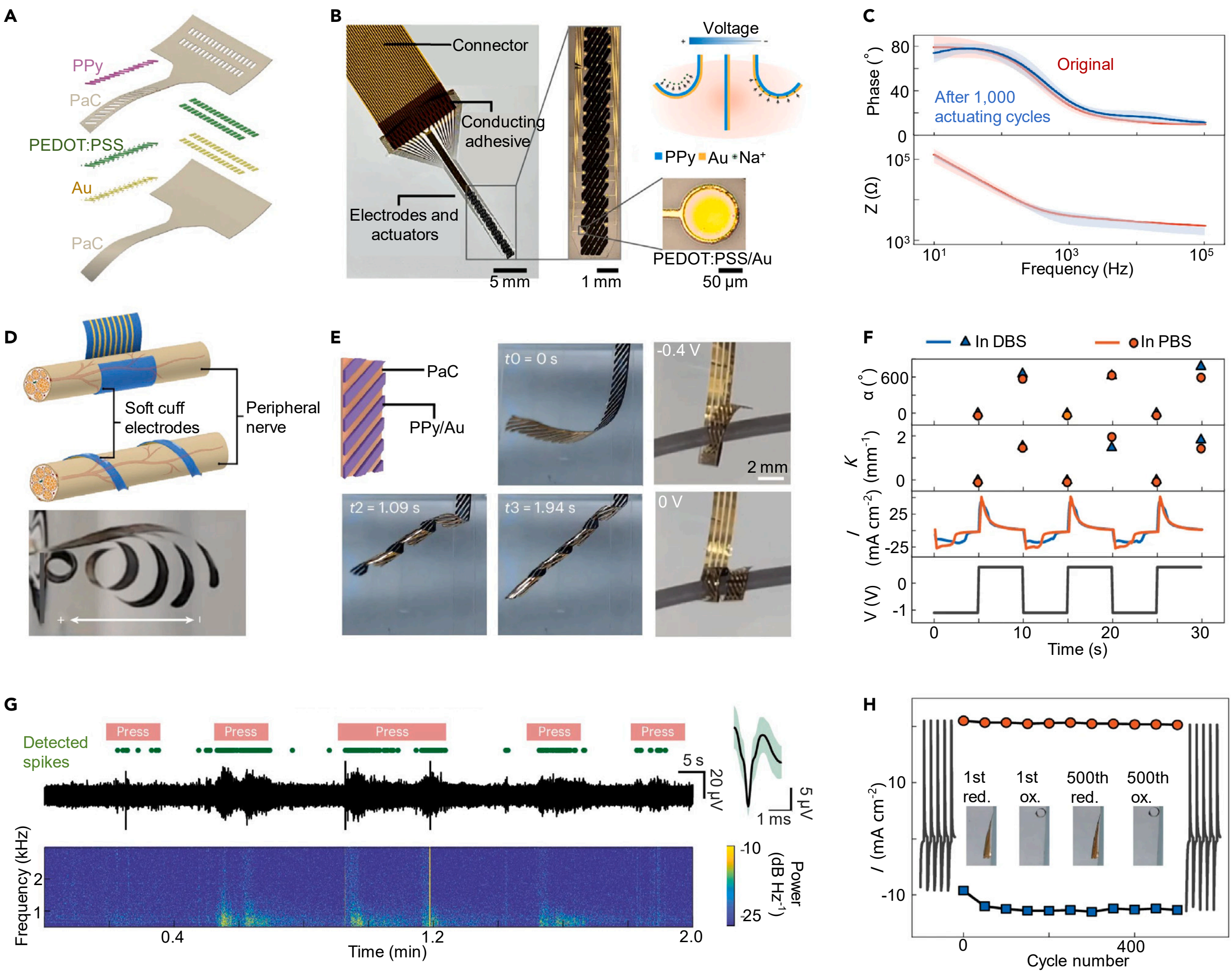

Figure 1. Soft cuff electrochemical actuators for minimally invasive peripheral nerve interfaces

(A) Structure of the soft nerve cuff electrode.

(B) Device connected to a flat flexible cable connector and bilayer PPy/Au actuating process.

(C) Impedance and phase of microelectrodes before and after 1,000 actuating cycles.

(D) Adaptive nerve cuffs in actuation and bending modes.

(E) Helical actuation of a PPy/Au cuff at 0.6 V and its wrapping around a 1.4 mm phantom nerve.

(F) Device performance in dodecylbenzene sulfonate sodium solution versus phosphate-buffered saline.

(G) Trace from the sciatic nerve during hind paw pressing, with the average waveform displayed on the right.

(H) Robustness of actuating cycles: Red and blue curves showing peak currents recorded every 50 cycles.

The key findings of this study illustrate that a soft nerve cuff actuator is capable of establishing and sustaining a stable, self-closing peripheral nerve interface, eliminating the necessity for surgical sutures or adhesives traditionally used to secure implanted bioelectronics in position. By leveraging soft actuators and flexible neural electrodes, the developed cuffs not only exhibit exceptional conformability but also possess the ability to dynamically adjust to the size and shape of the nerve, notably diminishing the likelihood of nerve injury during and after implantation.

However, integrating these electrically actuated neural electrodes into clinical practice while ensuring long-term safety and effectiveness presents several challenges: (1) Current understanding suggests that the immune response and material degradation could significantly influence the long-term efficacy of the implanted neural electrodes. Therefore, it is crucial to develop advanced materials that can withstand physiological degradation while maintaining optimal functionality.[8] (2) Typical photolithography and metal deposition processes cannot currently be successfully employed as methods to provide nerve cuff adaptability to individual anatomical structures. Exploring 3D printing and automated manufacturing processes might provide scalable solutions tailored to individual needs.[9] (3) To achieve high fidelity in nerve signal recording and stimulation, it's necessary to overcome interference from both biological and external sources. Advanced signal processing techniques and machine learning algorithms could be employed to enhance the differentiation between genuine neural signals and artifacts,[10] enabling real-time adaptive filtering and improving the accuracy of neural decoding. Addressing these challenges would not only improve the functionality of nerve cuff electrodes but also ensure long-term reliability in dynamic biological environments, facilitating their widespread adoption in neuroprosthetics and adaptive bioelectronics.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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