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COMMENT

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Stretching boundaries in neurophysiological monitoring

Bo Hou | **Xiaogang Liu**

Department of Chemistry, National University of Singapore, Singapore, Singapore

Correspondence
Xiaogang Liu.
Email: chmlx@nus.edu.sg

Abstract

The most prevalent among nervous system tumors significantly jeopardize patient health. For nerve integrity preservation after tumor removal, continuous intraoperative neurophysiological monitoring (CINM) is indispensable during microsurgery. The paper highlights the articles about the development of a system that employs soft and stretchable organic electronic materials for CINM. This innovative system harnesses soft and stretchable organic electronic materials and deploys conductive polymer electrodes with low impedance and modulus. These electrodes facilitate uninterrupted near-field action potential recording during surgery, resulting in enhanced signal-to-noise ratios and reduced invasiveness. Additionally, the system's multiplexing capabilities enable precise nerve localization, even in the absence of anatomical landmarks.

KEYWORDS
conductive polymer electrodes, neurophysiological monitoring, organic electronic materials

Nervous system tumors are the most common type of tumors affecting the nervous system and pose a substantial threat to patients' health and well-being.[1,2] To preserve the structural and functional integrity of nerves after tumor removal, continuous intraoperative neurophysiological monitoring (CINM) is essential during microsurgical procedures. A collaboration between Wang and Li's research groups at Capital Medical University, in partnership with Bao's group at Stanford University, has led to a breakthrough for CINM.[3] This innovative system leverages soft and stretchable organic electronic materials and employs conductive polymer electrodes with low impedance and low modulus. These electrodes enable uninterrupted recording of near-field action potentials during microsurgery, leading to improved signal-to-noise ratios and reduced invasiveness. Moreover, this system boasts multiplexing capabilities that enable precise localization of target nerves even in the absence of anatomical landmarks.

In this system, poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS) was chosen as the electrode material because it has excellent electrical properties and biocompatibility. By blending PEDOT:PSS with a crosslinkable supramolecular additive, they were able to create ultra-thin rail-like electrodes that exhibited both high electrical conductivity and mechanical stretchability. These unique properties allowed the electrodes to be easily wrapped around the nerves, conforming to the complex nerve structure and establishing a close tissue-electrode interface (Figure 1). Furthermore, the covalent linkage between the polyrotaxane crosslinker and the elastomeric substrate provided strong anchoring of the PEDOT layer to the substrate, making it highly resistant to external abrasion and friction. Another significant

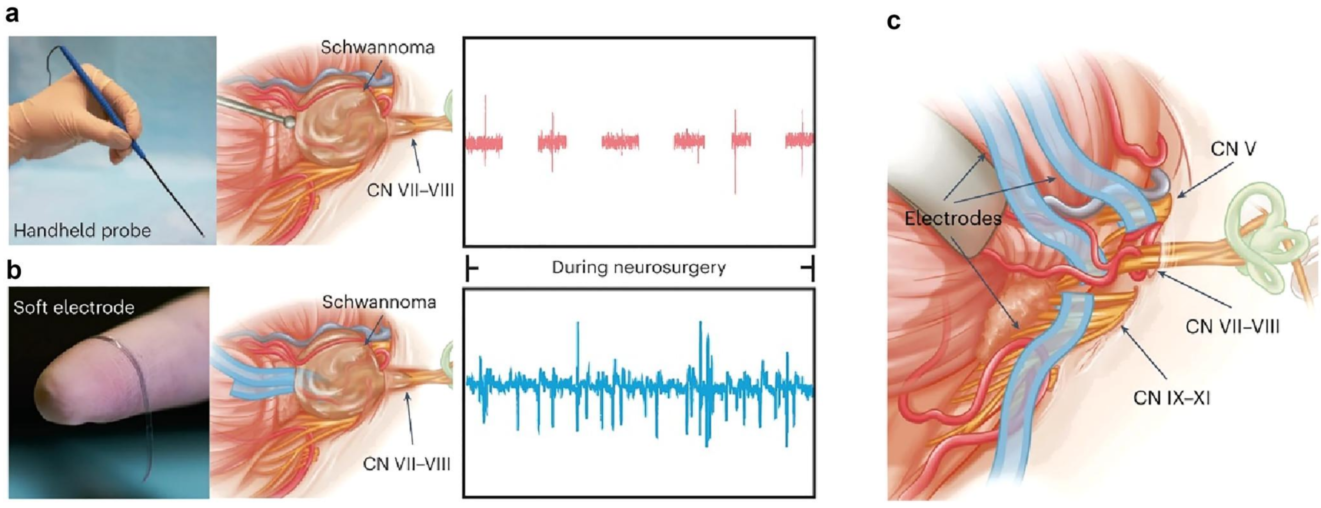

FIGURE 1 (a) Conventional handheld probe used for intraoperative neurophysiological monitoring (CINM), depicted in both photograph and schematic forms. (b) Photograph and schematic illustrating the innovative use of soft PEDOT electrodes for monitoring. Stable enclosure of nerves with PEDOT electrodes enables CINM during surgery. (c) Schematic portraying the design of soft PEDOT electrodes engineered for a comfortable neural interface. Reproduced with permission.[3] Copyright 2023, Springer Nature BV. PEDOT, poly(3,4-ethylenedioxythiophene).

advantage of the PEDOT electrodes was their ability to create multiplexed interfaces with different nerves. Using a simple one-step lithography process, numerous identical electrodes could be manufactured and wrapped around adjacent nerves. This multiplexing capability is a crucial step toward noninvasive neurodissection.

This innovation enabled continuous recording of near-field action potentials with high signal fidelity and minimal invasiveness during the intricate process of tumor resection surgery.[4–6] There was a notable decrease in postoperative morbidity observed in animal models. Moreover, aside from capturing neural physiological signals, low-impedance PEDOT electrodes facilitated functional stimulation to evaluate neural functionality during surgery. The authors also explored the synergy between these CINM modalities and targeted neurostimulation, underscoring the efficacy of their approach in restoring normal function following various neurosurgical procedures. The combination of CINM with precise micro-neurosurgical techniques served as a valuable safeguard against nerve injury during surgical interventions. The convergence of organic electronics and biology has led to hybrid systems where electronic components seamlessly interact with biological systems to enhance functionality. However, for organic electronic devices, conductivity, stability and compliance with biological systems are critical challenges. Moreover, rigorous biocompatibility testing is essential, including assessing tissue response, inflammation, and potential cytotoxicity when organic materials interact with biological systems.

Looking into the future, the continued refinement of electrode arrays that are durable, offer high resolution, possess soft and biocompatible qualities, and have neural stimulation and recording capabilities promises to expand their use in more complicated surgical disciplines.[7,8] However, it is important to acknowledge certain limitations associated with the clinical use of soft electrodes. One limitation is that soft electrodes are commonly applied to superficial nerves, making them less effective in penetrating deep tissues or nerves. Prolonged use can also be compromised by factors such as electrode displacement and wear, which can affect the precision of monitoring and stimulation. Although known for their favorable signal-to-noise ratio, data collected with soft electrodes may still be susceptible to motion artifacts. Precise electrode placement demands surgical expertise, adding complexity to procedures. Despite these challenges, we anticipate the emergence of advanced and versatile soft electrodes combined with novel biocompatible materials. This development will bring about a profound change in the field of neural monitoring and stimulation.

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CONFLICT OF INTEREST STATEMENT

Xiaogang Liu is on the editorial board of this journal and was not involved in the editorial review or the decision to publish this article. All authors declare no financial/commercial conflicts.

ORCID

Xiaogang Liu https://orcid.org/0000-0003-2517-5790

REFERENCES

1. K. D. Miller, Q. T. Ostrom, C. Kruchko, N. Patil, T. Tihan, G. Cioffi, H. E. Fuchs, K. A. Waite, A. Jemal, R. L. Siegel, J. S. Barnholtz-Sloan, *Ca-Cancer J. Clin.* **2021**, *71*, 381.
2. C. Horbinski, T. Berger, R. J. Packer, P. Y. Wen, *Nat. Rev. Neurol.* **2022**, *18*, 515.
3. W. Zhou, Y. Jiang, Q. Xu, L. Chen, H. Qiao, Y. X. Wang, J. C. Lai, D. Zhong, Y. Zhang, W. Li, Y. Du, X. Wang, J. Lei, G. Dong, X. Guan, S. Ma, P. Kang, L. Yuan, M. Zhang, J. B. Tok, D. Li, Z. Bao, W. Jia, *Nat. Biomed. Eng.* **2023**, 1. https://doi.org/10.1038/s41551-41023-01069-41553
4. D. Kiyasseh, R. Ma, T. F. Haque, B. J. Miles, C. Wagner, D. A. Donoho, A. Anandkumar, A. J. Hung, *Nat. Biomed. Eng.* **2023**, *7*, 780.
5. B. D. Paulsen, K. Tybrandt, E. Stavrinidou, J. Rivnay, *Nat. Mater.* **2020**, *19*, 13.
6. H. Hu, H. Huang, M. Li, X. Gao, L. Yin, R. Qi, R. S. Wu, X. Chen, Y. Ma, K. Shi, C. Li, T. M. Maus, B. Huang, C. Lu, M. Lin, S. Zhou, Z. Lou, Y. Gu, Y. Chen, Y. Lei, X. Wang, R. Wang, W. Yue, X. Yang, Y. Bian, J. Mu, G. Park, S. Xiang, S. Cai, P. W. Corey, J. Wang, S. Xu, *Nature* **2023**, *613*, 667.
7. Y. Liu, J. Liu, S. Chen, T. Lei, Y. Kim, S. Niu, H. Wang, X. Wang, A. M. Foudeh, J. B. Tok, Z. Bao, *Nat. Biomed. Eng.* **2019**, *3*, 58.
8. Y. Jiang, Z. Zhang, Y.-X. Wang, D. Li, C.-T. Coen, E. Hwaun, G. Chen, H.-C. Wu, D. Zhong, S. Niu, *Science* **2022**, *375*, 1411.

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