



## Interfacing with the Peripheral Nervous System



This Special Issue is dedicated to the development of the peripheral nerve interface (PNI). Fifty years have passed since the first clinical implementation of a PNI in humans, and just ten years have passed since the launch of the Defense Advanced Research Projects Agency (DARPA) Reliable Neural-Interface Technology initiative (RE-NET). In this past decade, the pursuit of a more reliable means to communicate with the peripheral nervous system has evolved into a vast multi-disciplinary effort, confronting surgical, medical, engineering, and software challenges while catalyzing rapidly maturing technologies. The span of this work is reflected in this Special Issue; we have compiled reports of new electrode technologies (Elyahoodayan et al., 2020; Kim et al., 2020; Yu et al., 2019), new neuromodulation approaches (Cotero et al., 2020), advances in wireless integration (Deshmukh et al., 2020; Sivaji et al., 2019), new implantation strategies (Chapman et al., 2019; Dingle et al., 2020; Spearman et al., 2020), algorithmic solutions for signal drift (Davey et al., 2020) and interference removal (Levy et al., 2020), new modeling approaches (Khadka et al., 2019) and even whole-system level results showing a PNI prosthesis in the field (George et al., 2020). Many of these reports are the products of ongoing DARPA programs for peripheral nerve research and application, revisited here by Naufel et al. (2020). The Electrical Prescriptions (ElectRx) program focuses on nerve engagement to treat clinical disease. The Targeted Neuroplasticity Training (TNT) program concentrates on pairing nerve stimulation with training to facilitate the rapid learning of new skills. The Hand Proprioception and Touch Interfaces (HAPTIX) program develops resources for motor control and sensory feedback to and from prosthetics via PNI technologies. Together these programs have provided funding and focus on the challenges of PNI development. The results are leading to advances not only in technology, but also in fundamental science, contributing to global efforts outside of the DARPA purview.

The breadth of research expertise in this field has produced innumerable advances but also given rise to a vast degree of wide-ranging knowledge and diverse approaches. We hope by publishing this Special Issue to draw attention to these incredible discoveries of the past few years and to collect in one place a series of best practice recommendations as a valuable resource for PNI researchers. Among the compiled reports are key insights on surgical techniques (Dingle et al., 2019), on mapping fascicular connections (Thompson et al., 2019), on identifying dorsal horn neurons (Smith et al., 2020), on blocking mammalian motor nerves (Bhadra et al., 2020), and evaluating vagal nerve involvement in gastric stimulation (Ward et al., 2020). In addition, invited authors present comprehensive reviews on somatic neuroprostheses (Raspovic et al., 2020) and PNI design (Larson and Meng, 2020), as well as guides on clinical translation (Charkhkar et al., 2019) and assessment of chronic PNI safety (Shafer et al., 2019).

Despite the rapid and renewed focus on PNI development, and

enormous promise, clinical usage of PNIs remains uncommon for bioelectric medicine and rare for prosthetic control. Major challenges remain to be solved. These include the development of a PNI capable of functioning for a human lifespan, the ability to selectively target individual fascicles non-destructively, a completed map of human fascicular anatomy, and others, in addition to various remaining technical and ancillary obstacles. These hurdles are daunting but clearly surmountable given the tremendous work of the past ten years. Moreover, the potential good that may continue from this research far outstrips the effort and funding still required. Millions of patients may soon find relief from chronic pain, or restoration of function, as a result of the work published here and yet to come.

We would like to thank the participating authors for their contributions and the Journal of Neuroscience Methods for hosting this Special Issue. We hope the enclosed articles provide insights and inspirations for researchers and practitioners.

## References

- Bhadra, N., Foldes, E.L., Gerges, M.R., Ackermann, D.M., Kilgore, K.L., 2020. Counted cycles method to measure the block inception time of kilohertz frequency mammalian motor nerve block. *J. Neurosci. Methods* 333, 108561. <https://doi.org/10.1016/j.jneumeth.2019.108561>.
- Chapman, C.A.R., Smith, T.M., Kelly, M., Avery, J., Rouanet, T., Aristovich, K., Chew, D.J., Holder, D.S., 2019. Optimisation of bioimpedance measurements of neuronal activity with an ex vivo preparation of Cancer pagurus peripheral nerves. *J. Neurosci. Methods*. <https://doi.org/10.1016/j.jneumeth.2019.108322>.
- Charkhkar, H., Christie, B.P., Pinault, G.J., Tyler, D.J., Triolo, R.J., 2019. A translational framework for peripheral nerve stimulating electrodes: Reviewing the journey from concept to clinic. *J. Neurosci. Methods* 328, 108414. <https://doi.org/10.1016/j.jneumeth.2019.108414>.
- Cotero, V., Miwa, H., Graf, J., Ashe, J., Loghini, E., Di Carlo, D., Puleo, C., 2020. Peripheral Focused Ultrasound Neuromodulation (pFUS). *J. Neurosci. Methods*.
- Davey, C.E., Soto-Breceda, A., Shafton, A., McAllen, R.M., Furness, J.B., Grayden, D.B., Stebbing, M.J., 2020. A new algorithm for drift compensation in multi-unit recordings of action potentials in peripheral autonomic nerves over time. *J. Neurosci. Methods* 338, 108683. <https://doi.org/10.1016/j.jneumeth.2020.108683>.
- Deshmukh, A., Brown, L., Barbe, M.F., Braverman, A.S., Tiwari, E., Hobson, L., Shunmugam, S., Armitage, O., Hewage, E., Ruggieri, M.R., Morizio, J., 2020. Fully implantable neural recording and stimulation interfaces: Peripheral nerve interface applications. *J. Neurosci. Methods* 333, 108562. <https://doi.org/10.1016/j.jneumeth.2019.108562>.
- Dingle, A., Zeng, W., Ness, J.P., Albano, N., Minor, R.L., Feldman, C., Austin, M., Brodnick, S.K., Shulzhenko, N., Sanchez, R., Lake, W.B., Williams, J.C., Poore, S.O., Suminski, A.J., 2019. Strategies for interfacing with the trigeminal nerves in rodents for bioelectric medicine. *J. Neurosci. Methods* 324, 108321. <https://doi.org/10.1016/j.jneumeth.2019.108321>.
- Dingle, A.M., Ness, J.P., Novello, J., Israel, J.S., Sanchez, R., Millevolte, A.X.T., Brodnick, S., Krugner-Higby, L., Nemke, B., Lu, Y., Suminski, A.J., Markel, M.D., Williams, J.C., Poore, S.O., 2020. Methodology for creating a chronic osseointegrated neural interface for prosthetic control in rabbits. *J. Neurosci. Methods* 331, 108504. <https://doi.org/10.1016/j.jneumeth.2019.108504>.
- Elyahoodayan, S., Larson, C., Cobo, A.M., Meng, E., Song, D., 2020. Acute in vivo testing of a polymer cuff electrode with integrated microfluidic channels for stimulation, recording, and drug delivery on rat sciatic nerve. *J. Neurosci. Methods* 336, 108634.

- <https://doi.org/10.1016/j.jneumeth.2020.108634>.
- George, J.A., Davis, T.S., Brinton, M.R., Clark, G.A., 2020. Intuitive neuromyoelectric control of a dexterous bionic arm using a modified Kalman filter. *J. Neurosci. Methods* 330, 108462. <https://doi.org/10.1016/j.jneumeth.2019.108462>.
- Khadka, N., Truong, D.Q., Williams, P., Martin, J.H., Bikson, M., 2019. The Quasi-uniform assumption for Spinal Cord Stimulation translational research. *J. Neurosci. Methods* 328, 108446. <https://doi.org/10.1016/j.jneumeth.2019.108446>.
- Kim, H., Dingle, A.M., Ness, J.P., Baek, D.H., Bong, J., Lee, I.K., Shulzhenko, N.O., Zeng, W., Israel, J.S., Pisaniello, J.A., Millevolte, A.X.T., Park, D.W., Suminski, A.J., Jung, Y.H., Williams, J.C., Poore, S.O., Ma, Z., 2020. Cuff and sieve electrode (CASE): The combination of neural electrodes for bi-directional peripheral nerve interfacing. *J. Neurosci. Methods* 336, 108602. <https://doi.org/10.1016/j.jneumeth.2020.108602>.
- Larson, C.E., Meng, E., 2020. A review for the peripheral nerve interface designer. *J. Neurosci. Methods* 332, 108523. <https://doi.org/10.1016/j.jneumeth.2019.108523>.
- Levy, T.J., Ahmed, U., Tsaava, T., Chang, Y.C., Lorraine, P.J., Tomaio, J.N., Cracchiolo, M., Lopez, M., Rieth, L., Tracey, K.J., Zanos, S., Zanos, T.P., 2020. An impedance matching algorithm for common-mode interference removal in vagus nerve recordings. *J. Neurosci. Methods* 330, 108467. <https://doi.org/10.1016/j.jneumeth.2019.108467>.
- Naufel, S., Knaack, G.L., Miranda, R., Best, T.K., Fitzpatrick, K., Emondi, A.A., Van Gieson, E., McClure-Begley, T., 2020. DARPA investment in peripheral nerve interfaces for prosthetics, prescriptions, and plasticity. *J. Neurosci. Methods* 332, 108539. <https://doi.org/10.1016/j.jneumeth.2019.108539>.
- Raspopovic, S., Cimolatto, A., Panarese, A., Vallone, F., del Valle, J., Micera, S., Navarro, X., 2020. Neural signal recording and processing in somatic neuroprosthetic applications. A review. *J. Neurosci. Methods* 337, 108653. <https://doi.org/10.1016/j.jneumeth.2020.108653>.
- Shafer, B., Welle, C., Vasudevan, S., 2019. A rat model for assessing the long-term safety and performance of peripheral nerve electrode arrays. *J. Neurosci. Methods* 328, 108437. <https://doi.org/10.1016/j.jneumeth.2019.108437>.
- Sivaji, V., Grasse, D.W., Hays, S.A., Bucksot, J.E., Saini, R., Kilgard, M.P., Rennaker, R.L., 2019. ReStore: A wireless peripheral nerve stimulation system. *J. Neurosci. Methods* 320, 26–36. <https://doi.org/10.1016/j.jneumeth.2019.02.010>.
- Smith, T.M., Lee, D., Bradley, K., McMahon, S.B., 2020. Methodology for quantifying excitability of identified projection neurons in the dorsal horn of the spinal cord, specifically to study spinal cord stimulation paradigms. *J. Neurosci. Methods* 330, 108479. <https://doi.org/10.1016/j.jneumeth.2019.108479>.
- Spearman, B., Kuliasha, C., Judy, J., Schmidt, C., 2020. Integration of Flexible Polyimide Arrays into Soft Extracellular Matrix-based Hydrogel Materials for a Tissue-Engineered Electronic Nerve Interface (TEENI). *J. Neurosci. Methods*.
- Thompson, N., Mastitskaya, S., Holder, D., 2019. Avoiding off-target effects in electrical stimulation of the cervical vagus nerve: Neuroanatomical tracing techniques to study fascicular anatomy of the vagus nerve. *J. Neurosci. Methods* 325, 108325. <https://doi.org/10.1016/j.jneumeth.2019.108325>.
- Ward, M.P., Gupta, A., Wo, J.M., Rajwa, B., Furness, J.B., Powley, T.L., Nowak, T.V., 2020. An emerging method to noninvasively measure and identify vagal response markers to enable bioelectronic control of gastroparesis symptoms with gastric electrical stimulation. *J. Neurosci. Methods* 336, 108631. <https://doi.org/10.1016/j.jneumeth.2020.108631>.
- Yu, X., Su, J.Y., Guo, J.Y., Zhang, X.H., Li, R.H., Chai, X.Y., Chen, Y., Zhang, D.G., Wang, J.G., Sui, X.H., Durand, D.M., 2019. Spatiotemporal characteristics of neural activity in tibial nerves with carbon nanotube yarn electrodes. *J. Neurosci. Methods* 328, 108450. <https://doi.org/10.1016/j.jneumeth.2019.108450>.

Kee Scholten, Ellis Meng, Gretchen Knaack, Dong Song\*,  
E-mail address: [dsong@usc.edu](mailto:dsong@usc.edu) (D. Song).

\* Corresponding author