Electrophysiology Data Analysis for Connectomics: An Introduction

Data Science is Central for Advancements in Neuroscience

In 2018, *Nature Methods* published an article stating that “Neuroscience is experiencing a revolution” [1]. The article introduced a novel computational approach, implementing a neural network-based model to infer dynamics between active brain cells. As developments in neuroscience continue to unfold, that article is one of many suggesting that computing, automation, data analysis, and machine learning will increasingly be at the core of major research achievements and clinical applications in neuroscience.

Since the design of the transformer architecture in 2017 [2] and commercialization of scaled machine learning in recent years, large language models (LLMs) have rapidly become a ubiquitous technology [3]. Though much public attention and industry effort has focused on LLMs and other consumer-facing tools, some of the greatest achievements in machine learning are outside the scope of these applications. For example, machine learning applications have made major contributions to computational biology. In that domain, the AlphaFold algorithms have implemented a model similar to the transformer to increase the number of all known protein structures in the world from less than a few hundred thousand to hundreds of millions [4], [5]. Just as some of the next decade’s greatest achievements in biology and neuroscience will require applications of data science and machine learning, some of the greatest opportunities to innovate with data science and machine learning lie in applications to other fields, including biology and neuroscience.

Artificial neural networks (ANNs) are not the only technology showing promise for innovative applications to neuroscience. As the nervous system contains a network of connected, interacting neurons, known as a connectome, network science is similarly applicable. Network science provides a mathematical foundation for modeling and analyzing connectomes [6]–[8], including metrics (e.g., centrality, modularity) and algorithms (e.g., page rank and Louvain) for understanding individual nodes (neurons) and their communities within the network [7], [8]. The foundation of network science is combined with ANNs in graph neural networks (GNNs), including graph autoencoders (GAEs), which use convolutions on a product of the graph’s adjacency matrix, degree matrix, and node feature embeddings to establish structure-aware embeddings of each node [9], [10]. As modern methodological advances increase capacity for collection of high-resolution connectomes, these network science tools are already beginning to be applied to improve understanding of nervous tissue function (e.g., [11], [12]).

This review considers the intersection of subfields in data science and neuroscience, including connectomics, extracellular electrophysiology, brain computer interfaces, neural signal processing, and spike train analysis. In introducing these subfields, I suggest that they have significant potential for synergy in accelerating understanding of microscale processing and distributed systems in the brain. In addition to providing understanding, I propose that these same technologies will offer significant new clinical interventions for a wide variety of nervous system diseases and disorders in coming decades.

A Connectome Details Neural Connections

The term ”connectome” refers to the set of all neural connections in the nervous system, originating in the context of post-human-genome-project “-omics” research [13]–[15]. The term ”biological neural network” (BNN) [16] is also used to reference neural connections, though a BNN may be only a sub-network of the full network–a partial connectome. The field of connectomics is based on a foundational premise that the aggregated structure and function of individual neural connections determines intermediate- and high-level functionality of the brain, including cognitive, behavioral, and neurological outcomes. These aggregated neural connections can be considered as a network, with neurons as nodes and relationships between nodes as edges. Relationships are directional and may be excitatory, inhibitory, or modulatory, with relationship strength varying with the quantity of neurotransmitter released from one cell and the expression of neurotransmitter receptors on the other. Many factors at systemic and subcellular scales regulate the network as it changes over time [13]. Though a full connectome ideally includes all neurons and all synaptic relationships, connectomes are typically studied at varied scales. A partial connectome includes a sub-network of a complete microscale connectome; a macroscale connectome is a connectome without cellular resolution, resulting in analogs of a network science meta-node and some missing nodes or edges; and a functional connectome is based on functional relationships rather than known physical connections between cells [13], [17]–[20].

The gold standard for collection of a connectome is ex-vivo electron microscopy, a method that began to be used in the 1980’s [6], [21]. The process includes delicate slicing of the tissue and imaging of each slice, followed by stitching visualizations together to identify all neurons and connections. Current methods restrict the scale of this exercise to only small animal models such as C. elegans and drosophila melanogaster [6], [21], [22]. In larger mammals, ex-vivo microscopy has been used to produce partial connectomes from samples of neural tissue, and to produce macroscale connectomes from the full brain [23]–[25]. Ongoing methodological advances will likely continue to expand the scope and scale of these processes. While developments are promising, these methods are limited to only ex-vivo research, and microscopy-based connectomics must be combined with in-vivo neural recording to understand functional relationships and work toward clinical interventions.

A major milestone in connectomics was the Human Connectome Project (HCP) [20], which pioneered methods for collection of human connectomes in-vivo via magnetic resonance imaging (MRI), including functional MRI (fMRI) and diffusion MRI (dMRI). From 2010 to 2019, teams collected a large initial dataset of fMRI-based macroscale connectomes and standardized many processes for large-scale study with MRI. Many projects today continue to iterate and build on the HCP with expanded scope, considering additional populations and analyses. While these methods have proven extremely useful in many research cases, they observe neural activity only indirectly by measuring fluid flow through tissue. Measurement resolution is also restricted by the physical limitations of radiowaves used in MRI devices. As a result, cellular-level activity cannot be measured, and determination of causative relationships between nuclei is limited. For example, excitatory vs. inhibitory relationships typically cannot be identified [26].

Extracellular Electrophysiology Can Be Optimized for Resolution and Coverage

Recent advances in electrical engineering and data analysis for in-vivo neural recording adds complementary value to the contributions being made by current microscopy and MRI methods. Neural recording enables more specific identification of functional relationships between cells for a given human or animal during a given period in time, which will likely elucidate cellular underpinnings of high-level function of the nervous system, and build toward improved clinical interventions for many neurological and psychiatric disorders [27]–[30]. Important considerations with these advances in neural recording include: (1) recording should have sufficient resolution in space and time to differentiate precise firing activity of individual cells; (2) though whole-brain-recording is unlikely, a maximal spatial area should be targeted, to capture activity from many neurons, including those in different anatomical regions [31]; (3) the connections determined by analysis of the recordings will give functional, not necessarily anatomical, relationships [13]; and (4) collected data must be organized to enable efficient, scalable processing [32], [33].

Neural recording with a single electrode and a small sample of neural tissue has been used for nearly a century to understand the nervous system [34], [35]. As methods have evolved and used in animal models, much data has been collected and used to improve understanding about neurons and the brain [36], [37]. During the mid-20th century, methods for preparation and use of electrodes were refined and standardized to optimize accuracy and precision of recorded signals [38], [39]. Later, multiple electrodes were combined into single devices (e.g., tetrodes) to allow parallel recording at multiple adjacent sites. This enabled greater signal reliability and coverage of multiple cells, exposing the need for efficient and scalable data processing [37], [40], [41]. More recently, Neuropixels probes have been developed to record from hundreds of simultaneously-active channels, each associated with more than one thousand sites available on the hardware after implantation. Multiple probes can be inserted into the brain during an experiment, allowing for simultaneous recording from hundreds to thousands of neurons in-vivo in animal models and in humans [31], [36], [42], [43]. These developments over several decades show ongoing progress toward solving the previously stated problems of spatiotemporal resolution and coverage.

As the scope and scale of electrophysiology recording of the brain increases, devices for large-scale data collection are now being developed. In the 1990's, a seminal device was developed at the University of Utah to target a greater surface area ($\approx 4mm^2$) than would be feasible with single-shank devices by placing electrodes in a grid [44]. The greater coverage allowed more information transfer from the brain, powering a useful brain-computer interface (BCI). The Utah Array's technology has been used in humans with quadriplegia and amyotrophic lateral sclerosis (ALS) to control computers and a robotic arm, promising to improve quality of life after years of paralysis or difficulty moving. During initial studies, the device was implanted into the motor cortex, which directly controls voluntary muscle movement, but is not involved with planning or orchestrating movement [45]–[48]. The technology has been used to carry brain signals past a spinal injury to enable movement of a previously-paralyzed arm [49]. More recently, intracortical arrays have been implanted into brain regions outside the motor cortex that are associated with higher-level processing that leads to speech, improving communication for an ALS patient by decoding whole words [30]. Building on the Utah Array and similar intracortical devices, newer BCI devices continue to add more electrodes to optimize spatial resolution and coverage. New devices also implement flexible electrode materials with robotic insertion to optimize electrode placement and minimize impact on neural tissue, improving recovery time after the implantation procedure [29]. As high-bandwidth BCI's approach clinical availability, they will likely complement, and show potential to compete with, existing lower-bandwidth electrode-based medical devices, including vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS) [50]–[52]. While there is much work left to do, continued advances show potential that future applications will be available for a wide range of neurological, and eventually psychiatric, conditions.

Advances in Neural Signal Processing Enable Scaled Electrophysiology

Regardless of scale, the primary output of electrophysiological recording is a set of voltages, each associated with a time and a recording channel/site. Values are typically organized into a matrix with rows corresponding to channels and columns corresponding to timepoints. With hundreds of channels and thousands of timepoints per second, these matrices can become quite large, so they are often visualized as a heatmap (e.g., [32, Fig. 1A]). Initial processing of raw voltage data typically includes separation of the signal by wavelength with a high-pass filter to differentiate local field potential (LFP) voltages resulting from the local environment from action-potential (AP) voltages that correspond to neural firing. This step is often handled on-device for modern electrode technologies [31]. Next, AP values are often cleaned with transformations such as common average referencing and spatial whitening to resolve artifacts, noise, and movement of electrodes during recording [32], [53].

AP voltage data is often processed with an additional spike sorting algorithm to identify discrete spikes in the action potential signals and sort them into clusters, where each cluster is assigned spike times associated with a putative neuron. The spike times can be temporally binned into a binary vector known as a ”spike train”. Many spike sorting algorithms exist and vary by complexity [32], [41], [54]. For example, in some cases applications such as BCI’s where fast input/output is required, spikes may identified, but not sorted into clusters [29], [55]–[57].

A prototypical example spike sorting algorithm is KiloSort [32], [53]. In the KiloSort algorithm, AP voltage spikes are identified based on shifting values in adjacent spatiotemporal measurements (e.g., adjacent rows and columns in the AP space-by-time matrix). These adjacent measurements are vectorized and grouped by similarity via template deconvolution and clustering. Multiple iterations of template deconvolution and clustering have been implemented since 2016, with improvements including capacity for spikes to be split or merged in scenarios such as spike overlap [32], [53]. The KiloSort algorithm has been used for spike sorting in an animal model dataset collected over several years [36], [58] and featured in a standardized library of leading spike sorting algorithms [33]. As spike sorting algorithms continue to improve, precise identification of neurons and their spiking times will refine spike train analysis (described next) to enable analysis of neuronal network dynamics in-vivo and at scale.

Spike Train Analysis Produces Functional Connectomes

Using electrophysiology to identify discrete neurons and spiking events together with associated spatial positions in the brain may be the best way to gather high-resolution neural activity data for in-vivo research with animal models and clinical application to humans. Discrete spike data can be analyzed for insights into the network structure and dynamics underlying the activity. Recent work has applied modern ANN models to establish graph structure of a partial functional connectome (e.g., Vareberg et al. [59]), or to embed latent states of the network (e.g., latent factor analysis via dynamical systems, LFADS [1], [60]; Neural Encoding and Decoding at Scale, NEDS [28]). Other approaches for system-level analysis have included Bayesian, state-space, and linear system modeling [61]–[63]. Additionally, generalized linear models have been used to predict firing rate at the neuron-level [27], [64]. Here, we will consider two simpler algorithms, cross-correlation and transfer entropy, to build an initial intuition for more modern spike-train analyses.

Cross-correlation was one of the first spike train analysis algorithms to be developed [65]. This algorithm involves taking a sliding dot product based on the two spike trains (e.g., dot product of the last timepoint of train A and first timepoint of b, dot product of the last two timepoints of train A and first two timepoints of B). The sliding dot product produces a distribution that can be visualized as a histogram, termed a ”cross-correlogram”. If a peak or dip is found in the distribution by visualizing the histogram or by algorithmically identifying outliers, a synaptic connection is inferred. The amount and direction of offset of the spike trains can also be used to infer directionality of the synapse [27], [65], [66].

Within a few years of the publication of cross-correlation in the 1960’s, Granger causality was also developed and published [67]. Granger causality was originally developed for economics, but provided a generalizable method for infering relationships between time series. Decades later, transfer entropy was developed in the context of information theory, and offered a mathematically-related, non-parametric method similar to Granger causality [68]. Here we include the definition of transfer entropy in equation (1), adapted from [68, Eq. 4].

$$T_{X\to Y} = \sum_{y_t, y_h, x_h} p(y_t, y_h, x_h) \log_2 \frac{p(y_t \mid y_h, x_h)}{p(y_t \mid y_h)} \tag{1}$$

Transfer entropy adds directionality to a previous metric in information theory, mutual information [68]. When applied to spike train analysis, transfer entropy quantifies the amount of firing from neuron Y that is attributable to neuron X [27], [68].

Conclusion

This review considered foundations and recent advances in connectomics, neural electrophysiology, neural signal processing, and spike train analysis. The combination of knowledge and methods in these subfields is prime example of how modern data science and machine learning methods are accelerating achievements in other domains. As these subfields and their methods continue to develop, it is likely that they will lay a foundation for improving humankind's understanding of the distributed processing in our brains and offer promising therapies for treatment-resistant neurological and psychiatric diseases along the way.

References

[1] C. Pandarinath, D. J. O'Shea, J. Collins, *et al.*, "Inferring single-trial neural population dynamics using sequential auto-encoders," *Nature Methods*, vol. 15, no. 10, pp. 805–815, 2018, ISSN: 1548-7105. DOI: 10.1038/s41592-018-0109-9. [Online]. Available: https://doi.org/10.1038/s41592-018-0109-9.

[2] A. Vaswani, N. Shazeer, N. Parmar, *et al.*, "Attention is all you need," *arXiv preprint arXiv:1706.03762*, 2023. arXiv: 1706.03762 [cs.CL]. [Online]. Available: https://arxiv.org/abs/1706.03762.

[3] H. Naveed, A. U. Khan, S. Qiu, *et al.*, "A comprehensive overview of large language models," *ACM Trans. Intell. Syst. Technol.*, Jun. 2025, Just Accepted, ISSN: 2157-6904. DOI: 10.1145/3744746. [Online]. Available: https://doi.org/10.1145/3744746.

[4] J. Jumper, R. Evans, A. Pritzel, *et al.*, "Highly accurate protein structure prediction with alphafold," *Nature*, vol. 596, pp. 583–589, 2021, ISSN: 1476-4687. DOI: 10.1038/s41586-021-03819-2. [Online]. Available: https://doi.org/10.1038/s41586-021-03819-2.

[5] M. Varadi, D. Bertoni, P. Magana, *et al.*, "Alphafold protein structure database in 2024: Providing structure coverage for over 214 million protein sequences," *Nucleic Acids Research*, vol. 52, no. D1, pp. D368–D375, Jan. 2024, Published on behalf of Nucleic Acids Research, ISSN: 1362-4962. DOI: 10.1093/nar/gkad1011. [Online]. Available: https://doi.org/10.1093/nar/gkad1011.

[6] S. W. Emmons, "The beginning of connectomics: A commentary on white et al. (1986) 'the structure of the nervous system of the nematode caenorhabditis elegans'," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 370, no. 1666, p. 20 140 309, Apr. 2015, PMCID: PMC4360118, ISSN: 1471-2970. DOI: 10.1098/rstb.2014.0309. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4360118/.

[7] D. Easley and J. Kleinberg, *Networks, Crowds, and Markets: Reasoning About a Highly Connected World*. Cambridge, UK: Cambridge University Press, 2010, ISBN: 9780521195331.

[8] M. E. J. Newman, *Networks: An Introduction*. Oxford, UK: Oxford University Press, 2010, ISBN: 9780199206650.

[9] P. Veličković, G. Cucurull, A. Casanova, A. Romero, P. Liò, and Y. Bengio, "Graph attention networks," *arXiv preprint arXiv:1710.10903*, 2018. arXiv: 1710.10903 [stat.ML]. [Online]. Available: https://arxiv.org/abs/1710.10903.

[10] T. N. Kipf and M. Welling, "Variational graph auto-encoders," *arXiv preprint arXiv:1611.07308*, 2016.

[11] A. Srinivasan, R. Raja, J. O. Glass, *et al.*, "Graph neural network learning on the pediatric structural connectome," *Tomography*, vol. 11, no. 2, p. 14, 2025, Epub ahead of print: 2025-01-29, ISSN: 2379-139X. DOI: 10.3390/tomography11020014. [Online]. Available: https://doi.org/10.3390/tomography11020014.

[12] J. Neudorf, S. Kress, and R. Borowsky, "Structure can predict function in the human brain: A graph neural network deep learning model of functional connectivity and centrality based on structural connectivity," *Brain Structure and Function*, vol. 227, no. 1, pp. 331–343, 2022, Epub 2021-10-11, ISSN: 1863-2661. DOI: 10.1007/s00429-021-02403-8. [Online]. Available: https://doi.org/10.1007/s00429-021-02403-8.

[13] J. Ciarrusta and T. Arichi, "Chapter 1 - neurobiology and the connectome," in *Connectome Analysis*, M. D. Schirmer, T. Arichi, and A. W. Chung, Eds., Academic Press, 2023, pp. 3–23, ISBN: 978-0-323-85280-7. DOI: https://doi.org/10.1016/B978-0-323-85280-7.00012-9. [Online]. Available: https://www.sciencedirect.com/science/article/pii/B9780323852807000129.

[14] A. Mahapatra, "Omics in the postgenomic era," *ACS Chemical Biology*, vol. 5, no. 4, pp. 343–344, 2010, ISSN: 1554-8929. DOI: 10.1021/cb1000873. [Online]. Available: https://doi.org/10.1021/cb1000873.

[15] E. D. Green, J. D. Watson, and F. S. Collins, "Human genome project: Twenty-five years of big biology.," *Nature*, vol. 526, no. 7571, pp. 29–31, Oct. 2015, ISSN: 0028-0836. DOI: 10.1038/526029a. [Online]. Available: https://www.nature.com/articles/526029a.

[16] K. Yamazaki, V.-K. Vo-Ho, D. Bulsara, and N. Le, "Spiking neural networks and their applications: A review," *Brain Sciences*, vol. 12, no. 7, p. 863, Jun. 2022, E-published 2022 Jun 30. DOI: 10.3390/brainsci12070863. [Online]. Available: https://doi.org/10.3390/brainsci12070863.

[17] L. Baxter, "Chapter 3 - functional network construction using functional mri," in *Connectome Analysis*, M. D. Schirmer, T. Arichi, and A. W. Chung, Eds., Academic Press, 2023, pp. 45–69, ISBN: 978-0-323-85280-7. DOI: https://doi.org/10.1016/B978-0-323-85280-7.00002-6. [Online]. Available: https://www.sciencedirect.com/science/article/pii/B9780323852807000026.

[18] J. Blommaert and D. Christiaens, "Chapter 2 - structural network construction using diffusion mri," in *Connectome Analysis*, M. D. Schirmer, T. Arichi, and A. W. Chung, Eds., Academic Press, 2023, pp. 25–44, ISBN: 978-0-323-85280-7. DOI: https://doi.org/10.1016/B978-0-323-85280-7.00007-5. [Online]. Available: https://www.sciencedirect.com/science/article/pii/B9780323852807000075.

[19] T. J. Sejnowski, "Nanoconnectomics," in *Micro-, Meso- and Macro-Connectomics of the Brain*, H. Kennedy, D. C. V. Essen, and Y. Christen, Eds., Accessed via NCBI Bookshelf, Cham (CH): Springer, Mar. 2016, ch. 1, pp. 1–10. DOI: 10.1007/978-3-319-27777-6_1. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK435767/.

[20] J. S. Elam, M. F. Glasser, M. P. Harms, *et al.*, "The human connectome project: A retrospective," *NeuroImage*, vol. 244, p. 118 543, Dec. 2021, Epub 2021 Sep 8, ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2021.118543.

[21] J. G. White, E. Southgate, J. N. Thomson, and S. Brenner, "The structure of the nervous system of the nematode caenorhabditis elegans," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 314, no. 1165, pp. 1–340, Nov. 1986, ISSN: 0962-8436. DOI: 10.1098/rstb.1986.0056.

[22] L. K. Scheffer, C. S. Xu, M. Januszewski, *et al.*, "A connectome and analysis of the adult drosophila central brain," *eLife*, vol. 9, e57443, 2020, ISSN: 2050-084X. DOI: 10.7554/eLife.57443. [Online]. Available: https://doi.org/10.7554/eLife.57443.

[23] A. Motta, M. Berning, K. M. Boergens, *et al.*, "Dense connectomic reconstruction in layer 4 of the somatosensory cortex," *Science*, vol. 366, no. 6469, eaay3134, 2019. DOI: 10.1126/science.aay3134. eprint: https://www.science.org/doi/pdf/10.1126/science.aay3134. [Online]. Available: https://www.science.org/doi/abs/10.1126/science.aay3134.

[24] M. Helmstaedter, K. L. Briggman, and W. Denk, "High-accuracy neurite reconstruction for high-throughput neuroanatomy," *Nature Neuroscience*, vol. 14, no. 8, pp. 1081–1088, 2011, ISSN: 1546-1726. DOI: 10.1038/nn.2868. [Online]. Available: https://doi.org/10.1038/nn.2868.

[25] K. Amunts, C. Lepage, L. Borgeat, *et al.*, "Bigbrain: An ultrahigh-resolution 3d human brain model," *Science*, vol. 340, no. 6139, pp. 1472–1475, 2013.

[26] P. Hagmann, L. Cammoun, X. Gigandet, *et al.*, "Mr connectomics: Principles and challenges," *Journal of Neuroscience Methods*, vol. 194, no. 1, pp. 34–45, 2010, Proceedings of the Workshop "Neuroanatomical Tracing and Systems Neuroscience: The State of the Art", ISSN: 0165-0270. DOI: https://doi.org/10.1016/j.jneumeth.2010.01.014. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0165027010000361.

[27] R. Kobayashi and S. Shinomoto, "Inference of monosynaptic connections from parallel spike trains: A review," *Neuroscience Research*, vol. 215, pp. 37–46, 2025, Will BigData change Neuroscience? ISSN: 0168-0102. DOI: https://doi.org/10.1016/j.neures.2024.07.006. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S016801022400097X.

[28] Y. Zhang, Y. Wang, M. Azabou, *et al.*, "Neural encoding and decoding at scale," *arXiv preprint arXiv:2504.08201*, 2025. arXiv: 2504.08201 [q-bio.NC]. [Online]. Available: https://arxiv.org/abs/2504.08201.

[29] E. Musk and Neuralink, "An integrated brain-machine interface platform with thousands of channels," *Journal of Medical Internet Research*, vol. 21, no. 10, e16194, Oct. 2019, ISSN: 1438-8871. DOI: 10.2196/16194. [Online]. Available: https://www.jmir.org/2019/10/e16194/.

[30] N. S. Card, M. Wairagkar, C. Iacobacci, *et al.*, "An accurate and rapidly calibrating speech neuroprosthesis," *New England Journal of Medicine*, vol. 391, no. 7, pp. 609–618, 2024. DOI: 10.1056/NEJMoa2314132. eprint: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2314132. [Online]. Available: https://www.nejm.org/doi/full/10.1056/NEJMoa2314132.

[31] J. J. Jun, N. A. Steinmetz, J. H. Siegle, *et al.*, "Fully integrated silicon probes for high-density recording of neural activity," *Nature*, vol. 551, no. 7679, pp. 232–236, 2017, ISSN: 1476-4687. DOI: 10.1038/nature24636. [Online]. Available: https://doi.org/10.1038/nature24636.

[32] M. Pachitariu, N. A. Steinmetz, S. N. Kadir, M. Carandini, and K. D. Harris, "Fast and accurate spike sorting of high-channel count probes with kilosort," in *Advances in Neural Information Processing Systems*, D. Lee, M. Sugiyama, U. Luxburg, I. Guyon, and R. Garnett, Eds., vol. 29, Curran Associates, Inc., 2016.

[33] A. P. Buccino, C. L. Hurwitz, S. Garcia, *et al.*, "Spikeinterface, a unified framework for spike sorting," *eLife*, vol. 9, L. L. Colgin, S. Grün, and F. Kloosterman, Eds., e61834, Nov. 2020, ISSN: 2050-084X. DOI: 10.7554/eLife.61834. [Online]. Available: https://doi.org/10.7554/eLife.61834.

[34] M. Piccolino, "Luigi galvani and animal electricity: Two centuries after the foundation of electrophysiology," *Trends in Neurosciences*, vol. 20, no. 10, pp. 443–448, 1997, ISSN: 0166-2236. DOI: https://doi.org/10.1016/S0166-2236(97)01101-6. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0166223697011016.

[35] E. D. Adrian, *The Basis of Sensation: The Action of the Sense Organs*. New York: W. W. Norton & Company, 1928, Originally delivered as the Croonian Lectures of the Royal Society.

[36] I. B. Laboratory, "Data release - Brainwide map - Q4 2022," Nov. 2022. DOI: 10.6084/m9.figshare.21400815.v7. [Online]. Available: https://figshare.com/articles/preprint/Data_release_-_Brainwide_map_-_Q4_2022/21400815.

[37] M. A. Wilson and B. L. McNaughton, "Dynamics of the hippocampal ensemble code for space," *Science*, vol. 261, no. 5124, pp. 1055–1058, 1993. DOI: 10.1126/science.8351520. eprint: https://www.science.org/doi/pdf/10.1126/science.8351520. [Online]. Available: https://www.science.org/doi/abs/10.1126/science.8351520.

[38] R. M. Dowben and J. E. Rose, "A metal-filled microelectrode," *Science*, vol. 118, no. 3053, pp. 22–24, 1953, ISSN: 00368075, 10959203. [Online]. Available: http://www.jstor.org/stable/1680735 (visited on 07/18/2025).

[39] J. D. Green, "A simple microelectrode for recording from the central nervous system," *Nature*, vol. 182, no. 4640, p. 962, 1958, ISSN: 1476-4687. DOI: 10.1038/182962a0. [Online]. Available: https://doi.org/10.1038/182962a0.

[40] B. L. McNaughton, J. O'Keefe, and C. A. Barnes, "The stereotrode: A new technique for simultaneous isolation of several single units in the central nervous system from multiple unit records," *Journal of Neuroscience Methods*, vol. 8, no. 4, pp. 391–397, 1983, ISSN: 0165-0270. DOI: https://doi.org/10.1016/0165-0270(83)90097-3. [Online]. Available: https://www.sciencedirect.com/science/article/pii/0165027083900973.

[41] M. Jog, C. Connolly, Y. Kubota, *et al.*, "Tetrode technology: Advances in implantable hardware, neuroimaging, and data analysis techniques," *Journal of Neuroscience Methods*, vol. 117, no. 2, pp. 141–152, 2002, ISSN: 0165-0270. DOI: https://doi.org/10.1016/S0165-0270(02)00092-4. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0165027002000924.

[42] N. A. Steinmetz, C. Aydin, A. Lebedeva, *et al.*, "Neuropixels 2.0: A miniaturized high-density probe for stable, long-term brain recordings," *Science*, vol. 372, no. 6539, eabf4588, 2021. DOI: 10.1126/science.abf4588. eprint: https://www.science.org/doi/pdf/10.1126/science.abf4588. [Online]. Available: https://www.science.org/doi/abs/10.1126/science.abf4588.

[43] A. C. Paulk, Y. Kfir, A. R. Khanna, *et al.*, "Large-scale neural recordings with single neuron resolution using neuropixels probes in human cortex," *Nature Neuroscience*, vol. 25, pp. 252–263, 2022, ISSN: 1546-1726. DOI: 10.1038/s41593-021-00997-0. [Online]. Available: https://doi.org/10.1038/s41593-021-00997-0.

[44] E. M. Maynard, C. T. Nordhausen, and R. A. Normann, "The utah intracortical electrode array: A recording structure for potential brain-computer interfaces," *Electroencephalography and Clinical Neurophysiology*, vol. 102, no. 3, pp. 228–239, 1997, ISSN: 0013-4694. DOI: https://doi.org/10.1016/S0013-4694(96)95176-0. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0013469496951760.

[45] S.-P. Kim, J. D. Simeral, L. R. Hochberg, J. P. Donoghue, and M. J. Black, "Neural control of computer cursor velocity by decoding motor cortical spiking activity in humans with tetraplegia," *Journal of Neural Engineering*, vol. 5, no. 4, p. 455, Nov. 2008. DOI: 10.1088/1741-2560/5/4/010. [Online]. Available: https://dx.doi.org/10.1088/1741-2560/5/4/010.

[46] J. D. Simeral, Kim, S.-P., M. J. Black, J. P. Donoghue, and L. R. Hochberg, "Neural control of cursor trajectory and click by a human with tetraplegia 1000 days after implant of an intracortical microelectrode array," *Journal of Neural Engineering*, vol. 8, no. 2, p. 025 027, Mar. 2011. DOI: 10.1088/1741-2560/8/2/025027. [Online]. Available: https://dx.doi.org/10.1088/1741-2560/8/2/025027.

[47] L. R. Hochberg, D. Bacher, B. Jarosiewicz, *et al.*, "Reach and grasp by people with tetraplegia using a neurally controlled robotic arm," *Nature*, vol. 485, no. 7398, pp. 372–375, 2012, ISSN: 1476-4687. DOI: 10.1038/nature11076. [Online]. Available: https://doi.org/10.1038/nature11076.

[48] D. Bacher, B. Jarosiewicz, N. Y. Masse, *et al.*, "Neural point-and-click communication by a person with incomplete locked-in syndrome," *Neurorehabilitation and Neural Repair*, vol. 29, no. 5, pp. 462–471, 2015, PMID: 25385765. DOI: 10.1177/1545968314554624. eprint: https://doi.org/10.1177/1545968314554624. [Online]. Available: https://doi.org/10.1177/1545968314554624.

[49] A. B. Ajiboye, F. R. Willett, D. R. Young, *et al.*, "Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: A proof-of-concept demonstration," *The Lancet*, vol. 389, no. 10081, pp. 1821–1830, 2017, ISSN: 0140-6736. DOI: https://doi.org/10.1016/S0140-6736(17)30601-3. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0140673617306013.

[50] N. J. Pertsch, K. Sakakura, S. Sani, and J. Shils, "Neuromodulation for epilepsy," *The Neurodiagnostic Journal*, vol. 0, no. 0, pp. 1–21, 2025, PMID: 40607887. DOI: 10.1080/21646821.2025.2516861. eprint: https://doi.org/10.1080/21646821.2025.2516861. [Online]. Available: https://doi.org/10.1080/21646821.2025.2516861.

[51] C. N. Heck, D. King-Stephens, A. D. Massey, *et al.*, "Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: Final results of the rns system pivotal trial," *Epilepsia*, vol. 55, no. 3, pp. 432–441, Mar. 2014, Epub 2014 Feb 22. DOI: 10.1111/epi.12534. [Online]. Available: https://doi.org/10.1111/epi.12534.

[52] E. B. Geller, "Responsive neurostimulation: Review of clinical trials and insights into focal epilepsy," *Epilepsy & Behavior*, vol. 88, pp. 11–20, Nov. 2018, ISSN: 1525-5050. DOI: 10.1016/j.yebeh.2018.06.042. [Online]. Available: https://doi.org/10.1016/j.yebeh.2018.06.042.

[53] M. Pachitariu, S. Sridhar, J. Pennington, and C. Stringer, "Spike sorting with kilosort4," *Nature Methods*, vol. 21, no. 5, pp. 914–921, 2024, ISSN: 1548-7105. DOI: 10.1038/s41592-024-02232-7. [Online]. Available: https://doi.org/10.1038/s41592-024-02232-7.

[54] J. Boussard, C. Windolf, C. Hurwitz, *et al.*, "Dartsort: A modular drift tracking spike sorter for high-density multi-electrode probes," *bioRxiv*, 2023. DOI: 10.1101/2023.08.11.553023. eprint: https://www.biorxiv.org/content/early/2023/08/14/2023.08.11.553023.full.pdf. [Online]. Available: https://www.biorxiv.org/content/early/2023/08/14/2023.08.11.553023.

[55] S. Todorova, P. Sadtler, A. Batista, S. Chase, and V. Ventura, "To sort or not to sort: The impact of spike-sorting on neural decoding performance," *Journal of neural engineering*, vol. 11, no. 5, p. 056 005, Oct. 2014, ISSN: 1741-2560. DOI: 10.1088/1741-2560/11/5/056005. [Online]. Available: https://europepmc.org/articles/PMC4454741.

[56] B. P. Christie, D. M. Tat, Z. T. Irwin, *et al.*, "Comparison of spike sorting and thresholding of voltage waveforms for intracortical brain–machine interface performance," *Journal of Neural Engineering*, vol. 12, no. 1, p. 016 009, Dec. 2014. DOI: 10.1088/1741-2560/12/1/016009. [Online]. Available: https://dx.doi.org/10.1088/1741-2560/12/1/016009.

[57] E. M. Trautmann, S. D. Stavisky, S. Lahiri, *et al.*, "Accurate estimation of neural population dynamics without spike sorting," *Neuron*, vol. 103, no. 2, 292–308.e4, Jul. 2019, Copyright © 2019 Elsevier Inc. All rights reserved., ISSN: 0896-6273. DOI: 10.1016/j.neuron.2019.05.003. [Online]. Available: https://doi.org/10.1016/j.neuron.2019.05.003.

[58] I. B. Laboratory, "Spike sorting pipeline for the International Brain Laboratory," May 2022. DOI: 10.6084/m9.figshare.19705522.v4. [Online]. Available: https://figshare.com/articles/online_resource/Spike_sorting_pipeline_for_the_International_Brain_Laboratory/19705522.

[59] A. D. Vareberg, I. Bok, J. Eizadi, X. Ren, and A. Hai, "Inference of network connectivity from temporally binned spike trains," *Journal of Neuroscience Methods*, vol. 404, p. 110 073, 2024, ISSN: 0165-0270. DOI: https://doi.org/10.1016/j.jneumeth.2024.110073. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0165027024000189.

[60] M. R. Keshtkaran, A. R. Sedler, R. H. Chowdhury, *et al.*, "A large-scale neural network training framework for generalized estimation of single-trial population dynamics," *Nature Methods*, vol. 19, no. 12, pp. 1572–1577, 2022, ISSN: 1548-7105. DOI: 10.1038/s41592-022-01675-0. [Online]. Available: https://doi.org/10.1038/s41592-022-01675-0.

[61] E. N. Brown, L. M. Frank, D. Tang, M. C. Quirk, and M. A. Wilson, "A statistical paradigm for neural spike train decoding applied to position prediction from ensemble firing patterns of rat hippocampal place cells," *Journal of Neuroscience*, vol. 18, no. 18, pp. 7411–7425, Sep. 1998, ISSN: 0270-6474. DOI: 10.1523/JNEUROSCI.18-18-07411.1998. [Online]. Available: https://www.jneurosci.org/content/18/18/7411.

[62] L. Paninski, Y. Ahmadian, D. G. Ferreira, *et al.*, "A new look at state-space models for neural data," *Journal of Computational Neuroscience*, vol. 29, no. 1-2, pp. 107–126, Aug. 2010, ISSN: 1573-6873. DOI: 10.1007/s10827-009-0179-x. [Online]. Available: https://doi.org/10.1007/s10827-009-0179-x.

[63] V. Geadah, A. Nejatbakhsh, D. Lipshutz, J. W. Pillow, and A. H. Williams, "Modeling neural activity with conditionally linear dynamical systems," *arXiv preprint arXiv:2502.18347*, 2025. [Online]. Available: https://arxiv.org/abs/2502.18347.

[64] L. Paninski, "Maximum likelihood estimation of cascade point-process neural encoding models," *Network: Computation in Neural Systems*, vol. 15, no. 4, pp. 243–262, 2004, PMID: 15600233. DOI: 10.1088/0954-898X_15_4_002. eprint: https://doi.org/10.1088/0954-898X_15_4_002. [Online]. Available: https://doi.org/10.1088/0954-898X_15_4_002.

[65] D. H. Perkel, G. L. Gerstein, and G. P. Moore, "Neuronal spike trains and stochastic point processes: Ii. simultaneous spike trains," *Biophysical Journal*, vol. 7, no. 4, pp. 419–440, 1967, ISSN: 0006-3495. DOI: https://doi.org/10.1016/S0006-3495(67)86597-4. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0006349567865974.

[66] G. P. Moore, J. P. Segundo, D. H. Perkel, and H. Levitan, "Statistical signs of synaptic interaction in neurons," *Biophysical Journal*, vol. 10, no. 9, pp. 876–900, 1970, ISSN: 0006-3495. DOI: https://doi.org/10.1016/S0006-3495(70)86341-X. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S000634957086341X.

[67] C. W. J. Granger, "Investigating causal relations by econometric models and cross-spectral methods," *Econometrica*, vol. 37, no. 3, pp. 424–438, 1969, ISSN: 00129682, 14680262. [Online]. Available: http://www.jstor.org/stable/1912791 (visited on 08/12/2025).

[68] T. Schreiber, "Measuring information transfer," *Phys. Rev. Lett.*, vol. 85, pp. 461–464, 2 Jul. 2000. DOI: 10.1103/PhysRevLett.85.461. [Online]. Available: https://link.aps.org/doi/10.1103/PhysRevLett.85.461.