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Previews

Explorers of the cells: Toward cross-platform knowledge integration to evaluate neuronal function

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In this issue of *Neuron*, Petersen et al. (2021) introduce CellExplorer, an open-source tool to integrate neurophysiological metrics of neuronal activity from circuits to behavior. Together with other neuroinformatic resources, it may facilitate community-based multidisciplinary characterization of brain cell types.

Ancient Buddhist and Hindu texts report the parable of a group of blind men coming across an elephant. Trying to identify the mysterious creature by touch, each of them gropes along different body parts, reaching no consensus. Every man maintains his perspective as absolute truth and they all miss the whole picture.

The brain is an elephant that neuroscientists grope blindly. Understanding brain function from neurons to behavior is challenging because there are several levels of functional hierarchies to unwrap. For instance, molecular expression profiles of single GABAergic and glutamatergic cells suggest the notion of neuron type specificity. However, morphological reconstruction and basic electrophysiological characterization of individual cells fail to establish a unified taxonomy, even for relatively homogeneous populations (Gouwens et al., 2020). Although linking neuronal firing with the oscillatory activity of the local microcircuit provides important classificatory hints, connecting effects brain-wide in a behaving organism requires further knowledge integration (Lapray et al., 2012). Yet analytical tools bridging across different levels are typically developed by individual labs and remain dispersed across platforms. The current issue of *Neuron* introduces CellExplorer (https://cellexplorer.org/), an open-source MATLAB-based resource to integrate neurophysiological metrics of neuronal activity from circuits to behavior (Petersen et al., 2021).

CellExplorer enables neuroscientists to evaluate electrophysiological data from individual neurons obtained *in vivo* with extracellular recordings. It offers standardized and flexible data structures, processing modules, and a powerful graphical interface. The tool extracts basic metrics of action potential waveform and intrinsic spiking dynamics, which provide an initial, broad characterization. Next, the relationships between the firing rate and timing of individual cells and ongoing oscillations are added. Integrating these measurements can inform the classification of extracellular recorded cells by using data obtained from alternative methods, such as single-cell recording and labeling with glass pipettes or cell-type-specific optogenetic tagging. CellExplorer allows supplementing data with additional classification tags either from the tool itself or from external resources. It includes ground truth from a variety of optogenetically identified GABAergic interneuron subtypes and principal cells from the mouse cortex and hippocampus, as well as other publicly available reference data.

The tool also permits mapping the multi-site electrode layouts for detailed assignment of different cells to recording locations. For instance, cells in superficial and deep layers of a particular brain structure can be conveniently identified. This, together with other resources to explore monosynaptic connections or to compare cell metrics calculated for different temporal intervals, promises a rather holistic evaluation of neuronal activity in a range of conditions. At the highest level is the behavioral quantification of the experimental subject. The flexible data structure allows adding several fields, including tracking of animal position or body parts, such as the pupil, as well as tags for a wealth of behaviorally derived information.

CellExplorer complements an increasingly rich ecosystem of neuroinformatic resources for characterizing neurons. These open access platforms equip researchers with unique exploratory tools (Figure 1). The molecular biology revolution ushered in the ability to sequence single-cell transcriptomes of entire brain regions, spawning public repositories to mine multi-omic datasets (e.g., https://nemoarchive.org) (Armand et al., 2021). Three-dimensional reconstructions of axonal and dendritic arbors, once limited to small samples due to the labor-intensive nature of manual tracing, are now publicly available in excess of 150,000 individual cells (http://neuromorpho.org) (Akram et al., 2018). Together with multiple initiatives from the Allen Brain atlas (https://portal.brain-map.org), these resources allow tracking different cell types by their projections and molecular identity. Multi-patch recordings in slices can complement the biochemical and morphological characterization of neurons with correlated intrinsic electrophysiology (e.g., https://gui.dandiarchive.org) (Lee et al., 2021). Linking neuronal properties to behavioral function requires the measurement of cell-identified activity *in vivo*, which has been possible to date only in the most intensively investigated neural systems, most notably the rodent hippocampal formation (Sanchez-Aguilera et al., 2021) and neocortex (Siegle et al., 2021).

The concurrent availability of large-scale public data and open-source analysis tools opens the prospect of enabling researchers

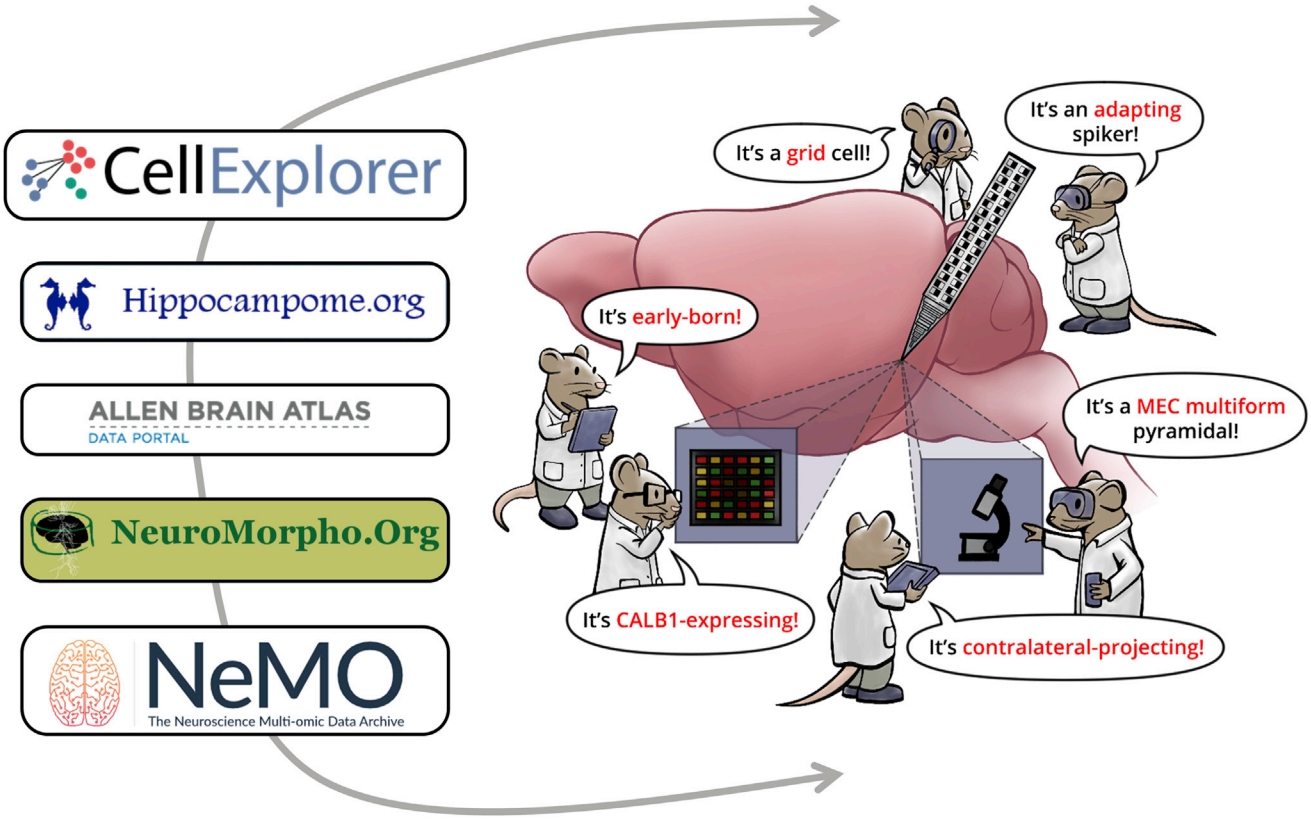

Figure 1. Cross-platform integration to explore neuronal function at multiple levels
The parable of the blind men and the elephant may well apply to brain research, if the evaluation of individual cells remains segregated at different levels. A medial entorhinal cortex (MEC) grid cell recorded *in vivo* looks like an adapting spiker when tested *in vitro* and has a multiform pyramidal morphology. These cells, grouped in clusters in layer II, are early-born and project to the contralateral MEC. Exploring brain cells with different tools may provide different but complementary perspectives. For example, knowing the recording location, the width of action potentials, the intrinsic firing pattern, and preferred phase relative to underlying network rhythms substantially narrows down the identity of possible neuron types. CellExplorer (https://cellexplorer.org) could draw information from NeuroMorpho.org (http://neuromorpho.org) to list all corresponding patterns of dendritic distributions and axonal projections, even those that were not directly observable from extracellular recordings. These data could then be utilized to reveal the likely presynaptic and postsynaptic partners via Hippocampome.org (http://hippocampome.org), in turn feeding the results to identify compatible spiking sequences from CellExplorer. In parallel, the neuron types consistent with these combined properties could provide the bases for searches in molecular databases such as the Allen Brain Atlas (https://portal.brain-map.org) and the NeMO Archive (https://nemoarchive.org) to help design further experiments with appropriate animal lines and related reagent arsenal. Drawing by Kyle Dise, George Mason University.

anywhere in the world to pursue novel analysis designs without an in-house experimental setup of their own. This will lead not only to a potentially multiplicative increase in the pace of discoveries, but also to a democratization of brain research thanks to lower financial, technological, and infrastructural requisites. However, it is essential to remember that neurons act in concert as parts of complex circuits. These platforms afford us a detailed yet fragmented view of the molecular expression, structural properties, biophysical features, developmental origins, connectivity specificity, and multiscale plasticity of neurons. While these data are sufficient to clearly demonstrate the humbling diversity of brain cells, our tendency to categorize neuronal properties along distinct dimensions is just an unfortunate distortion of empirical reductionism due to technological limitations. The computational roles of neurons emerge precisely and inextricably by the complex dynamic interactions among their biochemical, anatomical, and physiological mechanisms.

A positive attitude shift toward open-source software development and data sharing will ensure continuous progress in the detailed characterization of neuronal properties (Gleeson et al., 2017). An example is the recent investment of the U.S. National Institutes of Health in the multimodal classification of mammalian neurons, especially through the BRAIN Initiative Cell Census Network (BRAIN Initiative Cell Census Network (BICCN), 2021). The first coordinated effort of this large program focused on the primary motor cortex of human, marmoset, and mouse. The collaborative endeavor yielded an unprecedented comparative atlas integrating spatially resolved single-neuron transcriptomes, chromatin accessibility, DNA methylomes, whole-brain morphological reconstructions of long-range axons, electrophysiological recordings *in vitro*, and cellular resolution input-output mapping (BRAIN Initiative Cell Census Network (BICCN), 2021).

The BICCN results did not extend to *in vivo* electrophysiology, the purview of CellExplorer. Future breakthroughs will likely come from elucidating the synergistic relationships between neuronal properties across the physiological, molecular, and morphological dimensions in behaving

animals. Such advances entail a substantial effort toward cross-platform integration of the toolkit equipping our investigator's backpack (Figure 1). When characterizing the firing patterns of individual neurons in a cell assembly that represents a specific cognitive state, users of CellExplorer stand much to gain if they can probe the potential afferent and efferent connectivity of those neurons and the compositions of their protein machineries. In certain scenarios, it might also be useful to compare the emergent dynamics recorded *in vivo* to those observed in large-scale computational simulations based on data-driven models under the investigator's complete control. This may require radically new conceptual paradigms in the way we access and integrate knowledge from multiple sources.

Currently it is up to individual scientists to follow the chain of reasoning and switch back and forth among all available exploratory resources. It is still a time-consuming, incomplete, and error-prone process, with a high energy barrier for entry and a steep learning curve. These challenges can be alleviated by federating existing and forthcoming online tools and databases relevant to the study of neuron types, properties, and circuits. Future linkage by application programming interfaces and adoption of shared terminologies would be useful to achieve robust interoperability and to facilitate both human and machine accessibility to metadata.

Back to the parable of the blind men, there is no way to understand the brain without embracing its multiscale complexity. Touching one level at a time will never provide the whole picture. The moment is ripe to integrate knowledge across complementary perspectives and to pursue the synergistic, community-based exploration of the elephant.

DECLARATION OF INTERESTS

G.A.A. is consulting for Baylor College of Medicine, University of Washington, and University of Michigan. L.M.d.l.P. declares no competing interests.

REFERENCES

Akram, M.A., Nanda, S., Maraver, P., Armañanzas, R., and Ascoli, G.A. (2018). An open repository for single-cell reconstructions of the brain forest. Sci. Data *51*, 1–12.

Armand, E.J., Li, J., Xie, F., Luo, C., and Mukamel, E.A. (2021). Single-cell sequencing of brain cell transcriptomes and epigenomes. Neuron *109*, 11–26.

BRAIN Initiative Cell Census Network (BICCN) (2021). A multimodal cell census and atlas of the mammalian primary motor cortex. Nature *598*, 86–102.

Gleeson, P., Davison, A.P., Silver, R.A., and Ascoli, G.A. (2017). A commitment to open source in neuroscience. Neuron *96*, 964–965.

Gouwens, N.W., Sorensen, S.A., Baftizadeh, F., Budzillo, A., Lee, B.R., Jarsky, T., Alfiler, L., Baker, K., Barkan, E., Berry, K., et al. (2020). Integrated morphoelectric and transcriptomic classification of cortical GABAergic cells. Cell *183*, 935–953.e19.

Lapray, D., Lasztoczi, B., Lagler, M., Viney, T.J., Katona, L., Valenti, O., Hartwich, K., Borhegyi, Z., Somogyi, P., and Klausberger, T. (2012). Behavior-dependent specialization of identified hippocampal interneurons. Nat. Neurosci. *15*, 1265–1271.

Lee, B.R., Budzillo, A., Hadley, K., Miller, J.A., Jarsky, T., Baker, K., Hill, D., Kim, L., Mann, R., Ng, L., et al. (2021). Scaled, high fidelity electrophysiological, morphological, and transcriptomic cell characterization. eLife *10*, e65482.

Petersen, P.C., Siegle, J.H., Steinmetz, N.A., Mahallati, S., and Buzsáki, G. (2021). CellExplorer: A framework for visualizing and characterizing single neurons. Neuron *109*, 3594–3608.

Sanchez-Aguilera, A., Wheeler, D.W., Jurado-Parras, T., Valero, M., Nokia, M.S., Cid, E., Fernandez-Lamo, I., Sutton, N., García-Rincón, D., de la Prida, L.M., and Ascoli, G.A. (2021). An update to Hippocampome.org by integrating single-cell phenotypes with circuit function in vivo. PLoS Biol. *19*, e3001213.

Siegle, J.H., Jia, X., Durand, S., Gale, S., Bennett, C., Graddis, N., Heller, G., Ramirez, T.K., Choi, H., Luviano, J.A., et al. (2021). Survey of spiking in the mouse visual system reveals functional hierarchy. Nature *592*, 86–92.

Dynorphin, won't you myelinate my neighbor?

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Accumulating evidence supports the prevalence of experience-dependent oligodendrocyte precursor cell (OPC) differentiation and myelination in learning and memory. However, the mechanisms remain unknown. In this issue of *Neuron*, Osso et al., (2021) report that stress causes the secretion of dynorphin by unmyelinated axons, which induces OPC differentiation and myelination of neighboring axons.

Oligodendrocytes form myelin in the vertebrate central nervous system (CNS) by wrapping axons with a highly specialized and multi-layered lipid-rich membrane. Myelin provides metabolic support and enables saltatory conduction of action potentials; the latter increases action potential conduction velocity, reduces metabolic demands needed to sustain electrochemical gradients, and decreases space requirements. Together, this profound axoglial interaction permitted the evolution of a highly efficient and complex nervous systems. The formation of CNS myelin is mostly a postnatal event, coinciding with major developmental milestones, such as the acquisition of basic motor functions. However, myelination is also a lifelong process, with an expanding body of evidence supporting the existence of experience-dependent myelination during adulthood (Bonetto et al., 2021). For instance, various environmental stimuli and experiences, such as complex motor learning,