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Neural ensemble communities: open-source approaches to hardware for large-scale electrophysiology

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One often-overlooked factor when selecting a platform for large-scale electrophysiology is whether or not a particular data acquisition system is 'open' or 'closed': that is, whether or not the system's schematics and source code are available to end users. Open systems have a reputation for being difficult to acquire, poorly documented, and hard to maintain. With the arrival of more powerful and compact integrated circuits, rapid prototyping services, and web-based tools for collaborative development, these stereotypes must be reconsidered. We discuss some of the reasons why multichannel extracellular electrophysiology could benefit from open-source approaches and describe examples of successful community-driven tool development within this field. In order to promote the adoption of open-source hardware and to reduce the need for redundant development efforts, we advocate a move toward standardized interfaces that connect each element of the data processing pipeline. This will give researchers the flexibility to modify their tools when necessary, while allowing them to continue to benefit from the high-quality products and expertise provided by commercial vendors.

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Introduction

Major breakthroughs in neuroscience often occur shortly after new methods become available. Many investigators prioritize in-house tool building, since being the first to apply cutting-edge technologies frequently leads to high-impact publications. How does the hardware developed within individual laboratories make its way to the wider community? For the most part, companies invest the time and money required to polish researchers' prototypes, which they then distribute back to researchers. These products typically use proprietary schematics and source code, which prevents them from being modified by users and commercial competitors. Knowledge of key elements required to extend or adapt the technology is not available to end users who would like to do so.

In the recent past the benefits of having companies supply robust, well-documented devices have often outweighed the costs of dealing with closed hardware. Most scientists are happy to use commercial tools if they help generate useful data and are widely adopted by their peers. In some instances, though, relying on closed-source tools can hinder progress. When commercial hardware is treated as a 'black box,' it can limit scientists' understanding of the data being generated, as well as their ability to update hardware functionality in light of new experimental demands. Furthermore, tools from different companies — even those designed for the same purpose — are often incompatible with one another. Once a platform has been selected, future work may end up locked in to a particular data processing pipeline.

Recent advances in the domain of open-source design have increased the quality of tools built by scientists, extending their usefulness beyond their lab of origin. When designed properly, open-source hardware can combine the user-friendliness and dependability of commercial products with the high performance and flexibility of tools developed in-house. There are numerous examples of open-source software making an impact in neuroscience [1–3,4•,5–9], but open-source hardware has yet to take hold to the same degree. We expect that to change in the immediate future.

In this opinion piece, we outline the merits of open-source development schemes with respect to a widely used neuroscientific technique: high-channel-count electrophysiology. We argue that the vanishing differences in quality between open and closed recording

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systems no longer justify the higher cost, hardware lock-in, and lack of interoperability that reliance on commercial hardware entails. Standardizing the interfaces between elements of the electrophysiologist's tool chain could create a scenario in which open and closed hardware can flourish side by side. Regardless, we believe that in the long run, open-source initiatives in electrophysiology will lead to considerable productivity benefits for scientists — even those without an inclination toward engineering.

Electrophysiology is well-suited for an open development model

In the simplest case, recording electrical signals from the brain requires two conductors to measure a potential difference, a means of amplifying that difference, and a method to store changes in this signal over time. A century ago, nerve impulses were amplified using vacuum tubes and recorded on photographic film scanned behind a mercury column [10]. Today, mass-produced circuits costing a few dollars can be used to amplify neural signals and store them digitally. In recent years, there has been a push to record from dozens or hundreds of channels simultaneously in order to understand the brain at the network level [11••,12–14]. Furthermore, experimental designs now call for equipment that can precisely manipulate neural activity in real time, as well as record it [15–20,21•].

For the most part, these advances in recording and stimulation technology have occurred within individual labs, after which they were commercialized and distributed to a wider audience. Some of the major vendors of commercial electrophysiology data acquisition systems are Neuralynx, Plexon, Blackrock Microsystems, Multichannel Systems, Tucker-Davis Technologies, Ripple, and Axona. All of these systems are monolithic, meaning the hardware and software components sold by different companies are not interoperable. By giving researchers access to high-quality, professionally tested tools, as well as reliable support services, these companies have been essential for the proliferation of multichannel electrophysiology over the past two decades. However, it is no longer clear that these services should be provided exclusively by commercial entities.

We see three reasons why tool development and distribution for large-scale electrophysiology would benefit from an active open-source community:

1. Electrode technology is advancing rapidly. Experimenters using twisted-wire tetrodes are packing more electrodes into a smaller area [22–24], electrode arrays are becoming thinner and denser [25–29], and dynamically reconfigurable probes are in use *in vitro* [29] and under development *in vivo* [30]. Researchers need the flexibility to choose among these options, or to mix technologies within the same preparation. Companies that adopt proprietary standards restrict researchers' freedom. For example, when neural signal processing chips were introduced by Intan Technologies, vendors gave up the opportunity to rally around a common standard. These chips can amplify and digitize up to 32 channels of neural data in an 8 mm × 8 mm package (http://www.intantech.com) [31,32••]. When integrated into a 'headstage' (the interface that connects electrodes to a data acquisition system), Intan chips offer considerable advantages over the analog buffer amplifiers that were used previously. For this reason, nearly every major vendor now sells headstages that incorporate Intan chips. However, none of these headstages are interchangeable. Users are stuck with whatever connectors the vendors have chosen to provide, and cannot customize them without the help of the manufacturer.
2. On the software side, the requirements for analysis and visualization vary greatly between labs, and even between experiments. Specialized algorithms are needed to handle electrophysiological data, especially when closed-loop feedback is required. It is often impossible to predict which algorithms will work best before the experiments have been run. An example of this is online spike sorting, which allows researchers to analyze the activity of single neurons during an experiment [33–35]. A few commercial systems already implement spike sorting using algorithms that may not be fully disclosed. This makes it difficult or impossible to compare data collected across different labs [36,37••].
3. Electrophysiologists tend to be technically savvy and favor a 'do it yourself' approach to science. Some of this is cultural, but much of it is out of necessity. The complexity and fragility of neural systems has forced many electrophysiologists to develop customized hardware and software for their experiments. Unfortunately, very little of this development is currently shared, leading to a huge amount of redundant effort within and across laboratories. Even though every experiment has unique demands, the general requirements for electrophysiology are similar enough that scientists would benefit from a more generalized, open framework for acquisition and analysis. Because electrophysiologists are already so adept at tool-building, support and development efforts could be distributed throughout the community.

These reasons, which are not unique to extracellular electrophysiology, make it likely that a shift toward a more open development model will occur in the near future.

A brief history of open-source approaches to multichannel data acquisition

There have been several attempts to develop open-source recording platforms that are polished enough and sufficiently well-documented to propagate beyond the labs that invented them. This section is not meant to be an exhaustive list of such platforms; rather, we hope to provide examples of how shifts in technology created opportunities for scientists to improve on previously available systems. Figure 1 charts the changes that have occurred in the price and channel count of these systems over time.

A/D

One of the first advances that drove the need for high-channel-count extracellular electrophysiology was the introduction of tetrode recording technology [38,39]. By placing four tightly spaced electrodes at a single location in the brain, tetrodes increased the number of identified neurons that could be isolated. Early work with tetrodes was essential for improving our understanding of how the hippocampus represents the environment [40,41], but they also increased the number of simultaneously recorded channels required in any given experiment. In the early 1990s in Bruce McNaughton's lab at the University of Arizona, and later in his own lab at MIT, Matt Wilson (along with his graduate student, Loren Frank) designed and built 'A/D,' an open-source system capable of processing data from many tetrodes in parallel. The closed-source alternative, DataWave, lacked the flexibility required for tetrode recordings, and Dr. Wilson did not want his research to be tied to the destiny of a single company. Data collected with A/D has led to a number of important discoveries in the field of systems neuroscience [42–44].

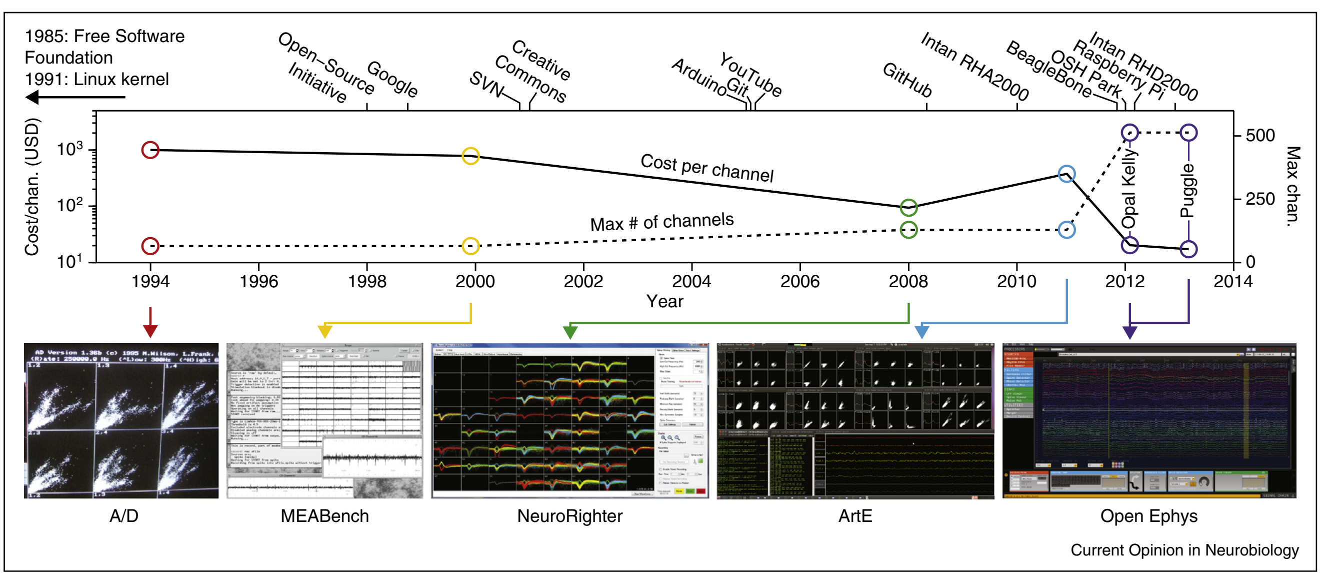
MEABench

Another domain that demands high channel counts is recording action potentials from cell cultures using planar microelectrode arrays (MEAs). In 1999, Daniel Wagenaar, Tom Demarse, and Steve Potter at Caltech created MEABench, a set of Linux command-line programs for acquiring, processing, and saving voltages from these arrays [45••] (http://www.danielwagenaar.net/res/software/meabench/). Each MEABench program applies a function, such as 'Filter' or 'Record,' to a multichannel data stream. A standardized interface allows programs to be daisy-chained and branched in order to construct complex signal processing pipelines. Although MEABench does not provide native support for closed-loop experiments, it can be combined with real-time stimulation tools to create feedback loops [45••]. MEABench has limited hardware driver support and currently only works with outdated and expensive Multichannel Systems data acquisition cards. However, the modularity and configurability of MEABench have inspired more modern open-source solutions.

NeuroRighter

In the mid-2000s, the introduction of high-channel-count analog-to-digital conversion hardware produced by National Instruments led the Potter lab to develop a

Figure 1



Timeline of open-source multichannel electrophysiology development. The improvements in usability, flexibility, and computational power of open-source multichannel data acquisition systems for electrophysiology have paralleled growth in open-source culture (e.g. the introduction of Arduino, Git, and YouTube in 2005) and technological developments within neuroscience (e.g. the introduction of Intan Technologies integrated bioamplifiers in 2009). In the last 20 years, the cost per acquisition channel has decreased by nearly two orders of magnitude while available channel counts have increased by approximately one order of magnitude. Standardization of hardware and software interfaces has allowed independent open-source hardware development projects to target common visualization software. For instance, the Open Ephys FPGA-based acquisition board and the ARM processor-based 'Puggle' (http://www.puggleboard.com) both target the Open Ephys GUI.

second open-source platform called NeuroRighter (https://sites.google.com/site/neurorighter/). NeuroRighter was created by John Rolston, Riley Zeller-Townson, and Jon Newman. This platform significantly reduced the cost of data acquisition for MEAs compared to MEA-Bench from around $60,000 to $10,000. To increase usability compared to MEABench, NeuroRighter operates as a standalone application with graphical control over filter and amplifier settings, online spike-sorting, data visualization, and data storage [46,47••]. Further, NeuroRighter integrated native support for real-time feedback. NeuroRighter's data processing pipeline can be augmented using an application programing interface (API) to create 'plugin' libraries that can be executed by NeuroRighter as it operates [47••]. The NeuroRigher API also supports electrical and optical stimulation protocols, making closed-loop experimentation possible.

ArtE

The A/D system worked reliably in the Wilson lab at MIT for over two decades, but it was only compatible with an outdated operating system (DOS) and obsolete computers. The increasing difficulty of obtaining replacement parts motivated a total rewrite of the underlying code for National Instruments hardware and GNU/Linux. This project, was named 'ArtE' (Almost real time Electrophysiology) to highlight the intention to provide closed-loop feedback (https://github.com/imalsogreg/arte-ephys). In addition to supporting equivalent features to A/D, ArtE was designed to run in parallel with an existing A/D system for the purpose of bootstrapping development and testing recorded spikes against a thoroughly debugged standard. The requirement to run alongside a very different system forced ArtE to be modular, with data moving between independent processes running on different machines over the network, in the spirit of MEABench. ArtE is still under active development, with large portions of its code written in Haskell to experiment with protection against bugs, crashes, and dead-locks.

Open Ephys

The public release of integrated amplifier chips by Intan Technologies [32••] made it possible to circumvent the National Instruments hardware that was a part of previous open-source platforms. The co-founders of the Open Ephys initiative (http://open-ephys.org), Josh Siegle and Jakob Voigts, two graduate students at MIT, designed a system based on these chips. The Open Ephys acquisition board featured both reduced hardware complexity and an order of magnitude drop in equipment cost compared to ArtE and NeuroRighter. Intan's development of open interfaces (RHD2000 SPI protocol and Rhythm FPGA firmware) made the development process much simpler. The low price of manufacturing acquisition boards (~$700 per unit in bulk) allowed Open Ephys to distribute 150 systems in less than a year. The Open Ephys platform also includes software that supports customizable data processing pipelines, similarly to MEABench.

What drove the development and adoption of these open-source tools? There are a few recent factors that have allowed open-source tools to rival and, in some ways, surpass the functionality of their commercial counterparts. First of all, thanks to their openness, all of the systems described above were facilitated by the advances of their predecessors. NeuroRighter was created to simplify MEABench, ArtE was inspired by the efforts of A/D and NeuroRighter, and the Open Ephys software began as a graphical interface for ArtE. Different requirements caused these systems to diverge, but they continue to serve different experimental requirements while benefitting from the cross-pollination of ideas.

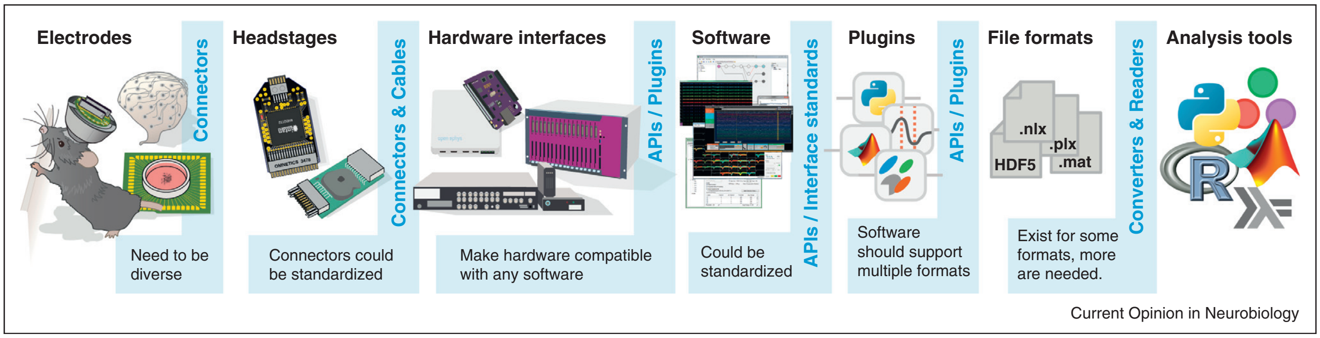
Advances in open-source tools for multichannel electrophysiology benefited from three technological and cultural developments occurring in parallel:

1. Smaller, cheaper, and better hardware. Market forces are pushing for ever-more compact and powerful components for mobile computers. Because these components are produced in huge volumes and provide substantial computational power, they can now fill the role of expensive application-specific integrated circuits (ASICs) for multichannel data acquisition and processing.
2. Tools for collaborative design. The rise of tools such as GitHub and Bitbucket (based on Git version control software) lowers the barriers to collaborative development. Additionally, wiki software allows documentation to be distributed throughout the community and continuously updated.
3. The open-source hardware movement. Products like Arduino (http://arduino.cc), Raspberry Pi (http://www.raspberrypi.org/), and Beaglebone (http://beagleboard.org/) make high-powered embedded computations more accessible. Many neuroscientists are introduced to hardware design through simple prototyping platforms like the Arduino, and subsequently graduate to more powerful systems. These devices set a precedent for what good open-source hardware design should be: powerful, simple to comprehend, highly adaptable, and well-documented.

Open interfaces: a middle-of-the-road solution

Taking cues from these widely adopted open-source platforms, we propose an approach to hardware development for extracellular electrophysiology that centers around standardized interfaces and modular architectures. The essence of this proposal is that the most common interfaces (e.g. electrode-to-headstage, headstage-to-cable, data-to-computer)

Figure 2



Key interfaces within multichannel electrophysiology platforms. Overview of the main components and interfaces in multichannel electrophysiology systems. Some components and interfaces need to be incompatible in order to comply with different requirements, such as electrodes and their connectors. Others, such as interfaces for software plug-ins or the interfaces between recording hardware and software, could be standardized with little additional development cost. The vertical text describes the interfaces that we recommend standardizing to improve the overall efficiency of our field.

should become standardized, so that anyone can make tools that fit into the same pipeline. In Figure 2, we illustrate some of the interfaces for large-scale electrophysiology that would benefit most from standardization.

It would be unwise to circumvent the expertise accumulated by existing companies. In a model where systems are modular, well documented, and interoperable, companies could concentrate their resources. Rather than developing and supporting entire platforms from top to bottom, they could focus on making the highest quality components within a modular system. This could occur in collaboration with the scientists that require new tools, or that have already built prototypes that are not ready for distribution. Additionally, standardization should create a market for supporting existing systems, in the same way that companies sell support contracts for Linux-based systems, rather than selling the software itself.

There is no fundamental reason why all the components of electrophysiology systems need to be open-source. In fact, most open tools currently make use closed-source integrated circuits. If each component were to be well-defined, with its interfaces documented and adherent to common standards, closed-source components would introduce less inflexibility into the complete system.

The same principle applies to the software used to record and process data. Currently, most software is closed-source and tied to commercial hardware, which leads to redundancy and lock-in. For the same reasons that we need modular hardware, modular software will become crucial in coming years. This is especially important given increasing popularity of real-time data processing in electrophysiology [21•,45••,47••,48]. Complex processing needs to be accomplished on the fly, and in close cooperation with the acquisition hardware. Modern processors are making it feasible to attain the real-time performance traditionally associated with low-channel-count systems (such as dynamic clamp) in a high-channel-count setting (see the Puggle at http://www.puggleboard.com and Open Ephys as http://open-ephys.org). Embedded CPUs and FPGAs provide the opportunity to merge hard real-time projects such as RTXI (http://rtxi.org) [49] with multi-channel systems like Open Ephys. This move toward real-time processing makes it even more important that algorithms and data interfaces become standardized and open. Otherwise it will become increasingly difficult to share custom data processing algorithms and to compare the results of experiments collected on different platforms.

Conclusion

Today, open-source electrophysiology systems tend to be cheaper and offer increased flexibility, while closed-source systems offer more robust hardware and professional support. But, as we have described, we anticipate that open hardware will continue to become more powerful, more accessible, and better supported in the near future. Scientists and funding agencies that stand to benefit from this progress should play a more active role in nurturing the maturation and proliferation of such tools.

One practical barrier to the spread of open-source hardware for electrophysiology is the lack of standardized interfaces. Pushing for the adoption of such interfaces wherever possible will improve the quality of open-source tools and allow open-source and closed-source tools to work together seamlessly. This would give electrophysiologists the option to employ custom-built solutions whenever necessary, while relying on commercial solutions at other points in the acquisition and analysis pipeline. In the rapidly changing landscape of extracellular electrophysiology, this model would reduce the need for the redundant development efforts that currently impede progress toward our ultimate goal: understanding the brain by eavesdropping on the electrical signals that underlie its functions.

Conflict of interest statement

Nothing declared.

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