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# Comprehensive chronic laminar single-unit, multi-unit, and local field potential recording performance with planar single shank electrode arrays

Takashi D.Y. Kozai[a,b,c,*], Zhanhong Du[a,b,c], Zhannetta V. Gugel[a,d], Matthew A. Smith[a,b,c,e], Steven M. Chase[b,f], Lance M. Bodily[g], Ellen M. Caparosa[g], Robert M. Friedlander[g], X. Tracy Cui[a,b,c]

[a] Bioengineering, University of Pittsburgh, United States
[b] Center for the Neural Basis of Cognition, United States
[c] McGowan Institute for Regenerative Medicine, University of Pittsburgh, United States
[d] Division of Biology and Biological Engineering, California Institute of Technology, United States
[e] Ophthalmology, University of Pittsburgh, United States
[f] Biomedical Engineering, Carnegie Mellon University, United States
[g] Neurological Surgery, University of Pittsburgh, United States

## HIGHLIGHTS

- Established new methods for analyzing depth dependent recordings.
- Optimized novel metrics for quantifying evoked MU and LFP recording quality and stability.
- Neural recording of resting state underestimates the number of neurons available for recording.
- Depth of cortical layer IV can fluctuate in the 1st wk after implantation, but stabilizes after 2 wks.
- There is strong dependence on the biological layers of the cortex on chronic recordings.

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## ABSTRACT

*Background:* Intracortical electrode arrays that can record extracellular action potentials from small, targeted groups of neurons are critical for basic neuroscience research and emerging clinical applications. In general, these electrode devices suffer from reliability and variability issues, which have led to comparative studies of existing and emerging electrode designs to optimize performance. Comparisons of different chronic recording devices have been limited to single-unit (SU) activity and employed a bulk averaging approach treating brain architecture as homogeneous with respect to electrode distribution.
*New method:* In this study, we optimize the methods and parameters to quantify evoked multi-unit (MU) and local field potential (LFP) recordings in eight mice visual cortices.
*Results:* These findings quantify the large recording differences stemming from anatomical differences in depth and the layer dependent relative changes to SU and MU recording performance over 6-months. For example, performance metrics in Layer V and stratum pyramidale were initially higher than Layer II/III, but decrease more rapidly. On the other hand, Layer II/III maintained recording metrics longer. In addition, chronic changes at the level of layer IV are evaluated using visually evoked current source density.
*Comparison with existing method(s):* The use of MU and LFP activity for evaluation and tracking biological depth provides a more comprehensive characterization of the electrophysiological performance landscape of microelectrodes.

* Corresponding author at: Department of Bioengineering, University of Pittsburgh, 5065 Biomedical Science Tower 3, 3501 Fifth Avenue, Pittsburgh, PA 15260, United States. Tel.: +1 4125438246.
*E-mail addresses:* tdk18@pitt.edu, tkozai@umich.edu (T.D.Y. Kozai).

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*Conclusions:* A more extensive spatial and temporal insight into the chronic electrophysiological performance over time will help uncover the biological and mechanical failure mechanisms of the neural electrodes and direct future research toward the elucidation of design optimization for specific applications.



## 1. Introduction

Recent advances in brain–computer interfaces (BCIs) have demonstrated restoration of functional motor control in study participants with tetraplegia (Collinger et al., 2012; Simeral et al., 2011). These studies used penetrating intracortical electrodes as the critical front–end interface components for extracting the intent of tetraplegic patients through the firing rate of individual or small populations of neurons and the discrete location of the recording electrode over the motor cortex map. This intent can then be used to control robotic arms over multiple degrees of freedom. While these studies have increased enthusiasm in clinical application, such as treating tetraplegia, it should be noted that reliable chronic electrophysiological recordings also play a critical role in advancing our understanding of basic neuroscience such as behavior, decision-making, memory, plasticity, neural circuitry and connectivity (Gage et al., 2010; Ganguly and Carmena, 2009; Guitchounts et al., 2013; Richardson et al., 2012; Stoetzner et al., 2010). In addition, these electrodes are valuable tools in understanding the impact of neurological diseases and injuries.

### 1.1. Current neural interface challenges

The variability and long-term reliability issues of electrode recording performance have been well characterized in the literature (Kozai et al., 2010; Rousche and Normann, 1998; Williams et al., 1999) (see Kozai et al., 2015b for review). Electrophysiology and histology results show significant differences in recording performance and tissue integration with the same device across different animals, different electrode shanks in the same animal, and at different recording depths on the same shanks (Kozai et al., 2010; Rousche and Normann, 1998; Stensaas and Stensaas, 1976; Williams et al., 1999; Woolley et al., 2013). Regardless of the technology used, the electrophysiological performance degrades over time, which further translates to drop in unit yield over time (Barrese et al., 2013; Chestek et al., 2011; Kipke et al., 2008). The current challenge is to develop technology and methodology to reduce the variability and improve the reliability and stability of implantable neural interfaces (Bjornsson et al., 2006; Gilgunn et al., 2012; Johnson et al., 2007; Karumbaiah et al., 2013; Kolarcik et al., 2014; Kozai et al., 2014a, 2014b; Kozai and Kipke, 2009; Kozai et al., 2012a; Kozai et al., 2014c; Kozai et al., 2010; Potter et al., 2013; Potter et al., 2012; Sawyer and Kyriakides, 2013; Saxena et al., 2013; Winslow et al., 2010).

### 1.2. Approaches and limitations for understanding chronic failure mechanisms

To address challenges with variability and long-term stability, engineers have developed new technology and methodology across a wide design space including footprint size (Kozai et al., 2012a), electrode site size (Kozai et al., 2012a), volumetric density across the array's footprint, strength (Kozai et al., 2012a), compliance/flexibility (Kozai et al., 2012a), elasticity/softness (Harris et al., 2011), electrochemical properties (Cui et al., 2001; Cui and Martin, 2003a, 2003b), device insertion speed (Bjornsson et al., 2006; Johnson et al., 2007), tip shape (Bjornsson et al., 2006), and surface chemistry modifications, such as anti-biofouling (Kozai et al., 2012a), anti-inflammatory (Zhong and Bellamkonda, 2005), or neuron-specific adhesion molecule surfaces (Azemi et al., 2011; Kolarcik et al., 2012). However, current approaches to studying the long-term stability has led to limited understanding of the relationship between device design and chronic recording performance:

(1) Many of these studies examined the tissue response to non-functional electrodes, thus limiting the understanding of the impact of these designs on electrophysiology, especially since recent study has shown that histology is a poor predictor for electrophysiological performance (Kozai et al., 2014c).
(2) For studies that include functional electrodes with electrophysiological evaluation, there is often a disconnect between technologies developed by engineers and the performance needs of scientists. New and existing technologies are often compared without regard to the layer from which the recording sites reside (Karumbaiah et al., 2013; Ward et al., 2009), which greatly bias the results (Kozai et al., 2014c), and can be misleading for understanding device design.
(3) As the interface between biology and technology begin to blur through advanced surface chemistry (Kozai et al., 2012a), drug-release (Luo et al., 2011), substrate dissolution (Gilgunn et al., 2012; Kozai et al., 2014b), tissue integration (Azemi et al., 2011), and stem cell seeding (Azemi et al., 2010; Purcell et al., 2009), it is important to explore the impact of these biotic technologies on brain function and the functional neural network in the microenvironment surrounding the probe.
(4) While SU may be the most sensitive assay, not all studies and applications require the use of SUs. For example, MUs are more commonly used in human/primate BCIs (Chestek et al., 2011; Collinger et al., 2012; Fraser et al., 2009; Hochberg et al., 2012). Different research and neuroprosthetic applications require different designs optimized for collecting specific type of data (MU, LFP) and when performance is evaluated by SU alone, it can add to the complexity of attempting to extrapolate impactful information on how electrodes can be designed to record reliably for long periods of time within specific application needs.

To address all these issues, the functional MU and LFP recordings are assessed using evoked cues. Evaluation of neural recordings with new technologies requires careful consideration of animal models. In primate BCI studies, monkeys have been shown to alter their brain activity to compensate for the shortcomings of online decoding algorithms (Chase et al., 2009; Jarosiewicz et al., 2008). In essence, when using a decoding algorithm that misinterprets motor intent, primates can 're-aim', or alter their intent, to compensate (Chase et al., 2012). For the purposes of testing the functional performance of new technology, we feel it is best to simplify the experimental and animal model to minimize the subject's ability to alter intent, particularly when the subject is not capable of effectively communicating how the intent and online decoding algorithm deviate. Furthermore, it is impractical to test every new technology in primates. Lastly, moving animals generate a considerable amount of electromagnetic motion artifact as tissue moves along the electrode/cables or as the headstage cables move, making it difficult to distinguish between electromechanical noise and