Title: What directions of improvements in electrode designs should we expect in the next 5-10 years?

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Introduction

Implantable neural bioelectronics are promising therapeutics for neurological disorders. Electrical stimulation via neural bioelectronics has been approved by the Food and Drug Administration as treatment for patients with hearing impairments, Parkinson's disease, epilepsy, and other physiological disorders. Additionally, neurotechnologies can detect local neuronal activities to restore function with external outputs. However, variability in the reliability of current electrode performances reduces their efficiency as therapeutic or research tools over chronic timescales. While the past 5-10 years of research has improved signal quality, resolution, and longevity of various types of neural electrodes, such as electrical, optical, and chemical electrodes, further developments in electrode design are required to advance scientific boundaries and clinical treatments. In this editorial, we explore emerging directions for electrode designs in the next 5–10 years.

Electrode designs

Recent efforts on microelectrode engineering has been to increase the communication bandwidth between the brain and computer system [1]. Therefore, one ambitious goal of electrode design is increasing the number of recording/stimulation sites to record and stimulate every neuron around the implanted probe. While it remains to be seen if interfacing every neuron is necessary for brain computer interfaces, improving channel count and density will advance our understanding of brain circuits and enable advance computational methods [1]. Currently, one of the electrode with the highest number of recording sites that is commercially available is the Neuropixel probe with 960 recording sites along a single 10 mm shank; although the site count is high, the probe's simultaneous recordings are limited by its 384 channels. Though, it is possible to increase the number of simultaneous recordings by implanting multiple Neuropixel probes [2]. More recently, a new electrode array by Neuralink contains 3072-electrode sites that are capable of recording and stimulation, although stimulation remains to be demonstrated in their recent work [3]. While these state-of-the-art probes have increased channel counts, it is also important to consider the increased data being generated from these recordings. The high bandwidth needed to transfer data leads to another limitation in current designs—wired connection and packaging [1]. Having a wired connection prevents subjects from freely moving and presents a potential point of origin for infection and mechanical failure, thus hindering quality of life and fundamental neuroscience research. However, a shift to wireless data transmission will result in lower bandwidth, higher power consumption, and increased heat generation which are issues that future designs must also mitigate [1]. Over the next 5-10 years, there is expected to be continued increased in number of electrode sites,

as well as advancement in wireless transmission and packaging that will enable increased freedom in individuals and improved bidirectional electrical communication between various nervous system regions and the neural interface.

As channel count of electrodes increase, another increasing concern is the impact of the device footprint on the foreign body response. The insertion of stiff materials into soft brain tissue elicits an inflammatory cascade that can contribute to poor long-term stability in electrical performances [1]. Therefore, soft, flexible materials are currently being incorporated in electrode designs to reduce mechanical strain and minimize chronic tissue damage caused by brain movement. While flexible materials have been shown to reduce inflammatory tissue response [4], these materials introduce new challenges such as motion-induced electromagnetic artifacts, water absorption, and increased delamination. Therefore, finding a balance between chronic tissue responses and impacted electrical properties of flexible electrodes remains a challenge. As these emerging challenges become more clearly characterized, there will likely be an increase in technological development aimed to address these new problems.

Optrode designs

One of the most exciting advances in neuroscience and technology design is optogenetics. Optogenetics is a technique that incorporates genes capable of expressing light-activated opsins and light-expressing proteins into targeted cells to allow highly selective neuromodulation and monitoring of cellular and molecular activity [5, 6]. In the last 5-10 years, combining optogenetics with electrical devices has expanded understanding of local neuronal circuit because of the ability to control stimulation with high spatiotemporal resolution and cell-type specificity. In turn, this has inspired a new generation of optrode designs aimed to address specific applications and answer specific scientific questions. However, challenges, such as thermal heat, optical coupling efficiency, light scattering, longevity of optical materials, and altered action potential threshold, impede chronic applications [7]. As a result, these issue remain complications that need to be mitigated in optrode designs.

In order to pinpoint neuronal activity evoked by optrode's optical stimulation, the light emission site on the probe should be proximal to recording sites [7], but distant enough to minimize photoelectric artifacts [8]. A current solution is to have a waveguide deposited onto the probe, which can guide the light from a distal light source to the tip of the shank where electrical contact sites are located. The benefits of waveguides are effective delivery of light to the stimulation site to enable high resolution of neural mapping, and customized light paths to allow multiple illumination sites [9, 10]. Alternatively coupling a bare laser diode chip as a light source to the waveguide allows fiberless optical stimulation, which is advantageous for free-moving animals and behavioral studies compared to tethered fibers [7]. Although, these devices are expensive and difficult to package, future waveguide-integrated optrode designs aim to directly combine the light source onto printed circuit board (PCB) [10]. While this introduces new challenges, advances in integrated circuit design onto PCBs are expected. Additionally, future improvements in optrodes are expected to focus on material and geometry design of waveguide for effective light delivery to brain tissue and perhaps improved spatial control over illumination. However, modifications to waveguide material and geometry affect irradiance, light scattering in tissue, numerical aperture, and thermal damage; therefore, optimal design parameters of waveguides will also require further investigation for device development.

An alternative strategy to advance optrodes is to have a light source directly applied onto the shank tip instead of light transmission by waveguides [1]. In comparison to the waveguide approach, direct combination of light sources can potentially achieve wireless optical stimulation because they have low power consumption. Moreover, this strategy enables decreased size and increased spatial control of simulation sites. One candidate light source for this strategy is GaN-based μLEDs because GaN is more biocompatible than alternative μLEDs and capable of delivering appropriate wavelengths of light needed to activate opsins while generating less thermal damage to surrounding tissue [11, 12]. However, stimulation artifacts induced by μLED crosstalk is an unavoidable challenge for this option. Alternatively, organic LEDs (OLEDs) are also favorable because they are flexible and have multi-wavelength emission to meet demands of brain electronics. However, OLEDs are susceptible to degradation by water and oxygen thus effective packaging is required to

ensure longevity [13]. Hence, improvements for optrodes in 5-10 years will likely include mitigation of simulation artifact, algorithms to differentiate electromagnetic artifacts, and packaging of light sources to improve functionality and longevity.

Chemical biosensors and Neurochemical modulator designs

Communication in the brain involves electrical and chemical signals. Notably, failure in regulating the brain's chemical signals is linked to etiologies of neurodegenerative diseases. Therefore, researchers have been developing chemical neural interfaces; electrochemical sensors to monitor neurochemicals, and drug-delivery devices to deliver chemicals into the brain. However, a number of limitations such as selectivity for biosensors and chemical storage for drug-delivery systems remain unaddressed.

Electrochemical biosensors detect target molecules based on current generated when the target molecules directly or indirectly carry out a redox reaction near the electrode's surface. These sensors generally have fast detection times ranging from ms to s [14]. However, they have poor selectivity and chronic in vivo performance due to interference from other electroactive chemicals in the surrounding area [1, 15]. Methods to improve selectivity include applying permeability-selective membranes, enzymes, nanoparticles, or aptamers to the electrodes [15, 16], but these solutions degrade over time. Hence, it is necessary that new designs devise methods to sustain selectivity agents, such as reloading. In the next 5-10 years, continuation of improvements in sensor materials and methods of selective coating—both critical components for augmentation of sensor selectivity and longevity—will continue to advance in vivo performance of neurochemical sensors.

Chemical stimulation of the brain can be performed through probes with chemical reservoirs. A recent development has allowed precise control of drug release and flow rates through a wirelessly controlled pump [17], which is important to prevent toxicity by overdose. Another benefit of these designs is their ability to integrate other modes of communication within the brain, such as electrical recordings [17, 18] or optical stimulation [18, 19]. Yet, many drug-delivery devices have limited capacities to reload or refill, which ultimately reduces the devices' longevity and chronic in vivo performance [20]. A possible solution is to develop refillable reservoirs [20]. Thus, with continued advancements in microelectromechanical systems and drug storage it is expected that there will be advances in chemical storage methods.

Conclusion

The three principle methods of interaction between neural interface technology and the brain are electrical, optical, and chemical. Advances expected in electrode designs include improvements in selectivity, spatial and/or temporal resolution, free-moving designs, and flexibility. Additionally, current electrode designs have started to incorporate multimodal recordings and stimulation methods on a single device [18, 19]. Multimodal electrodes will provide a novel way to observe and modulate the interplay between chemical and electrical signals in the brain. In addition, this is important for multi-modal validation of recordings and exclusions of artifacts that may be unique to a single recording modality. Therefore, it is expected that multimodal electrodes will accelerate the understanding of molecular and cellular mechanisms underlying normal and diseased brain physiology and provide a potential method for multimodal therapeutics of neural diseases. These trends will pave way for neural interfaces to further facilitate neuroscience research, improve in vivo performance, and perhaps, be expanded to clinical usage, leading to new breakthroughs in neuroscience and long-term treatment that are not yet possible with current neurotechnology.

Disclosure

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