Technologies to Interface with the Brain for Recording and Modulation

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"The history of electrophysiology has been decided by the history of electrical recording instruments."

Edgar Douglas Adrian (1932)

The desire to decipher targeted neural activities in the mammalian nervous system have inspired the development of many innovative technologies. These tools incorporate a variety of signaling modalities including electrical, chemical, and mechanical. While decades of neural engineering has been dedicated to electronic interfaces with neural tissue, more recent advances acknowledge the multiple modalities of neural activity and make use of additional interface methods, and in some cases, more than one interface method. Scaling of such technologies to acquire data from large numbers of neurons remains a challenge as does the longevity of interfaces in the presence of the foreign body response. The impact and significance of advancing interface technologies is not only to better understand proper function of the brain but to meet the unmet challenges posed by a variety of neurological, neurodegenerative, psychiatric, and neuromuscular conditions and deficits.

BRAIN COMPOSITION AND ANATOMY

The incredible anatomical and functional complexity of the brain poses a great challenge for engineering interfaces needed to record and modulate its activity with precision and over short and long time scales. The human brain (~1.3 cm^3) includes 100 billion (10^{11}) electrically active neurons (cell body ~20 μm diameter) that are interconnected to one another via chemically active synapses (20-40 nm wide gaps). Each neuron possesses on the order of 10^3 synapses and therefore 100 trillion (10^{14}) such connections exist within the brain. Furthermore, chemical synapses communicate via 10^2 different neurotransmitters with events occurring at a rate of 0.1-

200 Hz (“firing” rate). By comparison, the number of estimated stars in the observable universe is on the order of 10^{22}-10^{24}.

Electrically active neurons account for only 50% of the cells in the brain. The other 50% are electrically inactive support cells which include oligodendrocytes, astrocytes, and microglia (Chen et al. 2017). To support all of the cell types, the organ is bathed in and cushioned by cerebrospinal fluid and nourished via blood vessels.

Neurons are anatomically organized into different regions each having specific functions. Thus, interfaces to neurons naturally target specific brain regions associated with functions of interest. While it is possible to engineer devices that are smaller and computationally faster than neurons, we cannot fully recreate functional neural tissues. Hence, the ability to reliably interface with different brain regions is of immense scientific and clinical interest.

THE NATURE OF BRAIN ACTIVITY

Brain activity can be recorded from single neurons (single unit spikes or action potentials (AP)) or from groups of neurons (multi-unit recordings or local field potentials (LFP)) in a particular region. An inactive neuron has a resting potential of -70 mV (cell membrane voltage). An active neuron will exhibit an AP of 80-100 mV lasting a few milliseconds that propagates down a neuron. This measurable electrochemical gradient arises due to the cell’s selective permeability to specific ionic species mediated by voltage sensitive ion channels in the membrane and results in a measureable electrochemical gradient. At the synapse, the AP induces the release of neurotransmitters which cross the gap and bind to receptors on the cell membrane of the recipient neuron triggering opening of its ion channels. Signal transmission between two neurons connected by such a chemical synapse goes from electrical to chemical to electrical, where electrical signaling involves the movement of ions and not electrons. It is possible to

modulate this natural activity using artificial stimuli including the injection of current or chemical agents.

The AP or “spike” from a single neuron (single unit) represents communicative activity and is measureable using invasive electrodes placed within (intracellular) or next to (extracelluar) neurons. The “recording” electrode can be used in conjunction with a distant reference electrode; this pairing enables measurement of current or potential difference. Given the difficulty of targeting the interior of a single neuron, the destructive nature of such an interface, and the limited information this provides, the focus here will be on extracellular interfaces.

Alternatively, the LFP, the collective activity of a nearby group of neurons, can also be recorded with extracellular interfaces. Less invasive FPs can be recorded on the surface of the brain or through the protective dura membrane covering (electrocorticogram, ECoG) and also exterior to the skull (electroencephalogram, EEG). The less invasive the interface, the lower the resolution and higher the tissue volume from which recordings are obtained (e.g. ~0.1 mm for invasive penetrating electrode compared to 2 mm for ECoG and 10 mm for EEG (Borton et al. 2013)). With advances in recording interfaces, multiple penetrating electrodes can be placed to obtain recordings from multiple single units thus achieving both high resolution and access to information from different regions.

It should be noted that while most synaptic transmission is chemical in nature (involving neurotransmitters), there are also electrical synapses that form a mechanical and electrically conductive link via a structure known as a gap junction (~3-4 nm). There are also neurons that possess machinery that respond via specialized ion channels to physical stimuli including pH, temperature, pressure, and tension (Chen et al. 2017).

HISTORY OF ELECTRICAL STIMULATION AND RECORDING

Electrical interfaces that interact with the nervous system have been used since ancient times when Egyptians and Romans used electric shocks delivered by electric eels to treat pain. However, the foundations of bioelectricity, and electrophysiology date back to experiments conducted by Luigi Galvani in the 1780s in which dead frog leg muscles moved in response to current applied to nerves via metal wires, a phenomena dubbed "animal electricity." After the discovery of effects of electricity on the human body (usually on the investigator's own body), "medical electricity" research commenced (Bresadola 1998).

Giovanni Aldini, nephew of Luigi Galvani, discovered that electrical stimulation of the cerebral cortex could elicit physical responses – that of facial grimaces of decapitated prisoners (Aldini 1804). This discovery inspired work on brain stimulation to understand function and as a means of therapy. In 1938, Ugo Cerletti applied electric current to the skull to evoke "therapeutic" epileptic seizures to treat severe psychosis (Cerletti 1940). Another paradigm shift occurred in 1947 when electrodes were used for intraoperative electrical stimulation to determine the location of lesioned targets with the assistance of stereotactic techniques; up until that point, electrodes were used clinically to lesion the brain in neurosurgery (Spiegel et al. 1947). Brain stimulation was also investigated for pain control in the 1950s. Altogether, these efforts provided the foundation for new clinical therapies such as transcranial magnetic stimulation, cortical brain stimulation, and deep brain stimulation (DBS). DBS has borrowed heavily from cardiac pacemaker and defibrillator electrode concepts which were developed earlier.

Recordings of animal electricity were first reported by Leopoldo Nobili in 1828 using an electromagnetic galvanometer, but the first true recordings of the resting and action potentials were made in 1868 by Julius Bernstein using a differential rheotome that allowed measurement of fast electrical processes (Verkhratsky et al. 2006). The detection of currents from the brain

was achieved using an early form of EEG by Richard Caton in 1875 (Grimnes 2014). Wire electrodes were used to record from behaving animals in the 1950s. Advances in microelectronics led to the development of miniaturized multi-electrode arrays on planar surfaces in 1970s to interface with cell and tissue cultures and demonstrated that electrodes could be made at the scale of a single neuron. At about the same time, microelectrodes on penetrating probes were introduced. The technology was independently developed by multiple groups leading to commercially available products for research in animals and investigational studies in humans, including use in clinical trials in 2004 (Chen et al. 2017). While silicon microelectrode arrays have been developed over several decades, the inability to achieve reliable and stable long term device-tissue interfaces has spurred interest in the development of more compliant polymer probes.

Electrodes used for stimulation and recording have opposing requirements which prevent their simultaneous use. Smaller recording electrodes are preferred to isolate activity from single cells whereas stimulation electrodes should have larger surface area to increase the charge injection capacity available to excite neurons. Because electrical stimulation indiscriminately activates nearby neurons (excite activity) and produces a large artifact that interferes with recording, its use in understanding brain activity and therapy is limited; lowering the electrode area to minimize activation proportionately increases the input charge densities and the risk of of tissue damage. Electrical stimulation is unable to inhibit activity. These drawbacks of electrical interfaces have given rise to alternative interface modalities.

NON-ELECTRICAL INTERFACES

Advances in genetic engineering of cells have opened up new avenues to interface with neurons. In optogenetics, a neural population is genetically manipulated so that it can be selectively perturbed optically and probed electrically at the same time. This is accomplished by

introducing light-sensitive microbial ion channels to a cell called opsins which can change their conformation in response to light and affect ion transport. Unlike electrical stimulation, optogenetic approaches can both excite *and* inhibit neural activity.

Chemical stimulation can be achieved by infusing chemical agents or biological (genetic) agents to modulate activity. This is accomplished using conventional cannulae or microfluidics. Again, both excitatory and inhibitory modes can be accessed. Electrochemical sensors provide a means of detecting neurotransmitters and can be specific to particular electroactive neurotransmitters. These can be fabricated alongside conventional microelectrodes and provide information on the concentration of molecules.

Nanoscale transducers introduced into brain tissue can modulate brain activity through the conversion of optical, acoustic, and magnetic stimulation into voltage or electric fields. These nanotransducers include quantum dots, gold nanoparticles, up-conversion nanoparticles, and magnetic nanoparticles. Magnetic nanoparticles can activate mechano-sensitive ion channels by producing the required piconewton level forces in the present of a magnetic field gradient. The delivery of these nanomaterials and control of their targeting remains a challenge.

Interfaces need not be invasive. Acoustic waves and magnetic fields can be harnessed to modulate activity within the brain. Whereas electromagnetic waves in the visible and infrared spectrum have limited penetration depth (1 mm), transcranial focused ultrasound can access deeper regions (> 50 mm) although at inferior spatial resolution (1 mm^3). Transcranial magnetic stimulation can access the upper 10 mm but with reduced spatial resolution (Chen et al. 2017).

Although electrical and non-electrical interfaces are introduced separately here, several have been combined to leverage the advantages of the particular technique to enable multi-modal interfaces for research purposes.

CHALLENGES AND OPPORTUNITIES

The availability of appropriate interface technologies to the brain strongly affects our ability to understand it and develop new therapies. Even so, the limited and imperfect information that exists today has already resulted in clinically implemented technologies having only a few stimulating electrodes that have dramatically improved lives; DBS has U.S. Food and Drug Administration approval for the treatment of tremor (1997), Parkinson's disease (2002), dystonia (2003), and obsessive compulsive disorder (OCD, 2009) (Sironi 2011). Future advancements seek to seamlessly integrate neural interfaces with the brain such that *both* long term recording and modulation of neurons with a higher number of input and output channels can be obtained (Wellman et al. 2017). In order to achieve this, the health of the tissue-device interface needs to be improved by addressing tissue damage related to surgical delivery, the biological immune response, and stability of the materials used in construction of the interfaces. Likewise, further understanding of the effects that the complex interplay between material selection, device design, and realization through fabrication have on the long term performance and function of the device in the body is needed. These advances are critical to attaining chronically stable high density and large scale recordings. Similarly, modulation technologies need improvements in reliability and precision. When used together, recording and modulation can achieve exciting new concepts in closed-loop therapeutic systems of the future. While there are many exciting prospects for new therapies, the complexity of achieving stable neural interfaces combined with regulatory and reimbursement hurdles in the medical device space will continue to challenge innovators. With rigorous engineering focused on reliability, the next generation of life changing medical technology breakthroughs can be realized.

REFERENCES

Aldini G. 1804. Essai théorique et expérimental sur le galvanisme, avec une série d'expériences faites en présence des commissaires de l'Institut National de France, et en divers amphithéâtres anatomiques de Londres par Jean Aldini. Paris: De l'imprimerie de Fournier fils.

Borton D, Micera S, Millan J del R and Courtine G. 2013. Personalized neuroprosthetics. Science Translational Medicine 5(210):210rv212.

Bresadola M. 1998. Medicine and science in the life of Luigi Galvani (1737–1798). Brain Research Bulletin 46(5):367-380.

Cerletti U. 1940. L'elettroshock. Reggio-Emilia: Istituo psichiatrico di s. Lazzaro.

Chen R, Canales A and Anikeeva P. 2017. Neural recording and modulation technologies. Nature Reviews Materials 2:16093.

Grimnes S. 2014. Bioimpedance and Bioelectricity Basics. Boston, MA: Elsevier.

Sironi VA. 2011. Origin and evolution of deep brain stimulation. Frontiers in Integrative Neuroscience 5:42.

Spiegel EA, Wycis HT, Marks M and Lee AJ. 1947. Stereotaxic apparatus for operations on the human brain. Science 106(2754):349-350.

Verkhratsky A, Krishtal OA and Petersen OH. 2006. From Galvani to patch clamp: the development of electrophysiology. Pflügers Archiv 453(3):233-247.

Wellman SM, Eles JR, Ludwig KA, Seymour JP, Michelson NJ, McFadden WE, Vazquez AL and Kozai TDY. 2017. A materials roadmap to functional neural interface design. Advanced Functional Materials:1701269.