Advances and Development of Electronic Neural Interfaces

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Abstract – The discipline of neural engineering is working to enhance the functional and stability lifespan of present implanted neuroelectronic interfaces by developing next-generation interfaces employing biologically-derived and biologically-inspired materials. Humans and robots may exchange information using input devices like keyboards and touchscreens. Future information sharing may be facilitated through neural interfaces that provide a more direct electric connection between digital (man-made) systems and analog nerve systems. This paper presents the history and development of electronic brain interface; and classifies and analyzes the interfaces into four generations based on the technical landmarks within the electronic sensor interface and its evolution, including the patch clamp method, integrated neural interfaces, wearable or implantable neural interfaces, and multi-based neural interfaces. In this paper, we also discuss the potential presented by cutting-edge technology and critical system and circuit problems in the neural interface model.

Keywords – Foreign Body Reaction, Neural-Computer Interfaces, Electronic Neural Interfaces, Neural Interface Devices.

I. INTRODUCTION

The transmission of data from the nervous system to external devices is made possible through neuroelectronic interfaces, also known as brain or neural-computer interfaces. These tools typically take the shape of electrodes and are used to alter or record neuronal activities by transducing different cellular activities into applicable data (typically through recording) or by transmitting current into tissues (typically through stimulation). Clinical and research applications of neural interfaces include the restoration of hearing via cochlear implants, Parkinson's disease treatment by deep brain stimulation, and the direct operation of prosthetic limbs, including other peripheral equipment.

Sustaining functionality over extended periods of time in vivo is a critical design goal for implanted neural interfaces. The dynamic, aquatic environment provides a series of substantial difficulties that have hindered the neural interface performance, which meet these challenges head-on. A multimodal, long-lasting foreign body reaction (FBR) to the implants is the most common of these challenges, and it reduces the interface's effectiveness over time. Many studies have been conducted in an effort to mitigate the negative impacts of the FBR on device functionality by designing electrodes and implant techniques that target individual aspects of the FBR or at least mitigate their impact.

In this article, we provide a survey of FBR and its effects on the design of neural interface before delving into techniques for interfaces that are biologically active. These interfaces make use of materials that are either derived from or inspired by biology in order to facilitate better host-implant embedment and stabilized long-term electronic performance. Several systems that allow for interaction between people and the digital world have been created since the invention of the transistor in 1947. Keyboards, mice, and touchscreens are examples of input devices that efficiently convey human intent to a digital system. The ultimate objective of this kind of communication is to eliminate the need for such intermediary devices and instead create a direct line of communication between user intent (in the form of brain impulses) and the digital word. The development of silicon electronics has made feasible the use of neural interfaces. An individual's nervous system may communicate with an artificial device via a neural interface. The three main components of a typical interface are the electrical sensing interface, the tissue interface, and the brain signal processing unit. The evolution of the electronic sensing interface may be used to generally categorize brain interfaces into four generations.

Patch clamps were the first generation of devices that allowed for in vitro brain signal capture, but they needed elaborate protocols for preparing bio-samples before the analysis of signals. Multi-channel brain interfaces of the second generation made in-vivo studies possible, but the length of the cable connecting the in-vivo electrodes to workstations for the collection of data, processing of signals and control restricted the sorts of experiments that could be performed. The third generation of implantable/wearable devices, neural interfaces, and combined brain signal capture with wireless transmission to provide continuous activities in free-moving patients. Some gadgets were only wireless transmitters, but the more complex ones also included signal processing features, making them completely independent. Size and tissue injury were still issues since the electrodes were not integrated into the sensor module. The electrodes, electrode sensor interface (integrated with filters and low-energy amplifiers), and the units of signal processing, were all merged onto a similar substrate in the fourth generation neural interface identified as integrated neural interfaces. Because of this, ultra-small structures with high electrode densities and low power consumption are now possible.

In this article, we look back at the four generations of neural interfaces, discussing the successes and failures of each and the potential and problems presented by the current crop of devices. The remaining part of this article has been organized as follows: Section II presents a discussion of the history and development of electronic neural interfaces. Section III discusses the different types of neural stimulations. In Section IV, wearable/implantable neural interface devices are discussed. Lastly, Section V draws a conclusion to the article.

II. ELECTRONIC NEURAL INTERFACES

Neural interfaces have vast promise as prostheses, therapies, and scientific instruments, but they are just now starting to be explored. These devices offer a staggering range of potential uses and have already shown their transformative potential for amputees, quadriplegics, and people with neurological illnesses. Several of these wonderful examples, however, have a hard time being put into clinical practice because of issues with stability, repeatability, expense, the need for qualified personnel, and limitations on movement caused by benchtop equipment. It is obvious that current interfaces cannot achieve the performance that scientists and doctors hope for. It will take more than the gradual technical progress associated with Moore's law to transition from current devices to systems capable of providing even a fraction of the promise of brain interfaces (and its equivalents in for example wireless or battery technology). New research will need to be driven by visions that establish new objectives and potential routes to success.

Today's Neural Interfaces

It is generally agreed that Galvani's work with electrical stimulation were the first example of artificial neural interfaces, and that electrical neuromodulation (stimulation and blocking) continues to be the most common implanted clinical use. Most DBS devices for treating neurological conditions with known brain state associations (e.g., epileptic disease or depression, or Parkinson's disease), and chronic pain devices comprise of a small number of electrodes wired to a basic biphasic pulse generator with manual controls for frequency and amplitude.

Near Future Neural Interfaces

We envision a future where implantable devices can (i) record from thousands of neurons reliably over the course of years, (ii) interpret these signals in real time to identify behavioral and motor states or sensory inputs, and (iii) establish appropriate neuromodulation in a neurologically and therapeutically pertinent timescale (on the order of milliseconds). (ii) Initiating thousands of realistic pulse trains in target neurons (within a main nerve's mixed population) with minimal activation of non-target neurons and automated calibration of stimulation settings or invariant safe and effective whole-nerve stimulation. Brain regions or individual neurons may be stimulated or blocked over extended periods of time (ii). This chapter concentrates on the electronics components of ensuring this steady performance; however other chapters may address the electrodes and implant packing in more detail.

Recent advancements in electrode technology are reviewed in detail in [1], while extensive discussions of electrode packing may be found in [2]. As the number of channels increases and the connector and wire sizes get smaller, there are fundamental architectural challenges that must be overcome. For example, floating electrodes (i.e., with wires between the electrodes and electronics) already suffer from high interconnect failure rates, and this problem will only get worse as the number of channels increases. There are two clear options in the literature for high channel count devices: (1) abandoning floating electrodes and instead bonding electrodes directly to the neural interface IC via microfabrication techniques, or (2) employing a distributed architecture consisting of many small devices wirelessly linked together. The **Fig. 1** describes the motivating variables that should help the BMI community of brain-machine interfaces achieve these goals. This demonstrates how improvement in BMI systems is mostly driven by two different areas.

The contributions of fundamental neuroscience have been crucial to this development. Improved coupling to the human body is possible with more research into the neurological system, as well as the development of novel applications and sensory modalities. This encompasses a wide variety of research aims, such as those probing unique sensory systems and neurophysiology. Technology translation of electronic systems has also contributed to extremely quick advancements in the previous decade alongside these initiatives. The use of cutting-edge signal processing methods and CMOS microfabrication is only one way in which these systems test the limits of what is currently possible in integrated computing. As important as scientific advances in biomedical research have been, the enabling electronics have been much more pivotal. Hence, we emphasize three areas for development: circuit-level performance; designs and algorithms; and microfabrication.

Electro-physiology, the study of the electronic elements of tissues and cells, is crucial to the creation of electronic brain interfaces. Electrophysiology has been studied since the 18th century, during which Luigi Galvani used a Leyden jar to apply nerves charges of the muscles of dead frogs and record their contractions. It was not until the middle of the twentieth century when really game-changing capacities emerged, however. Electrochemical gradients of potassium and sodium ions over the membranes of the nerve cell were first recorded by Andrew Huxley and Alan Hodgkin in 1949, thanks to the invention of voltage clamp technology.

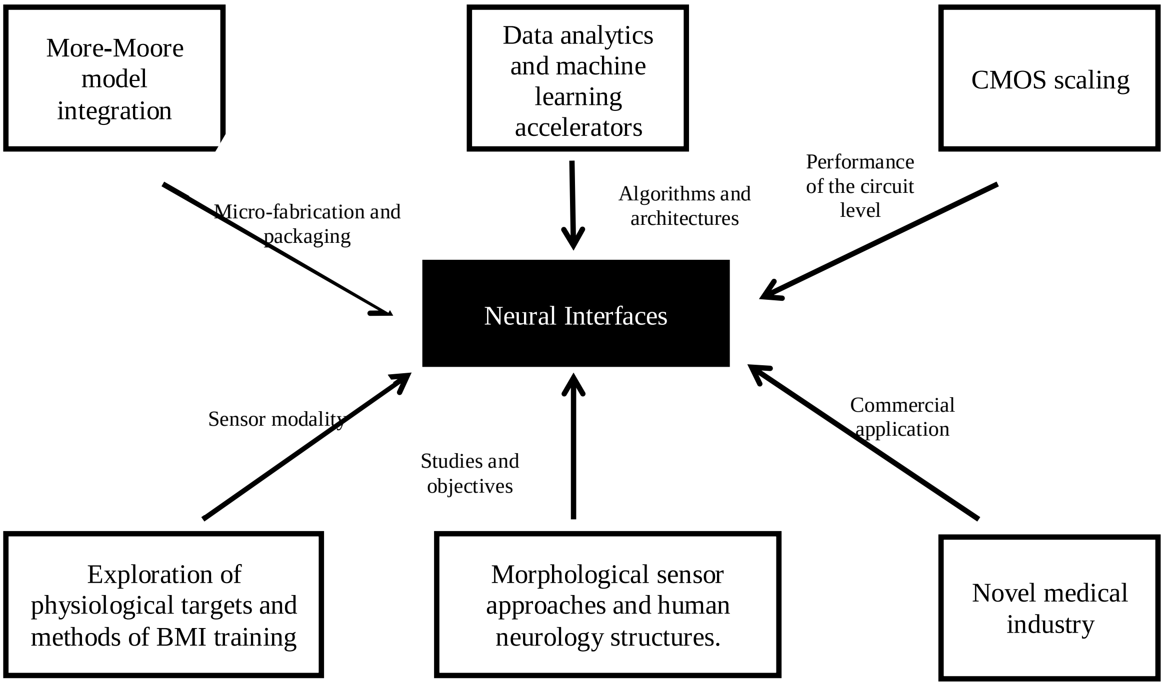

Fig 1. Major Factors Affecting the Enhancement of Edge Neural Interfaces

The membrane potentials were first described theoretically in 1952 by Hodgkin and Huxley, who used an RC (resistor-capacitor) circuit model. The patch clamp method for recording signals from individual ion channels was invented in 1976 by Gong, Yang, and Ma [3]. An enhanced patch clamp approach with significantly high resistance was conveyed in 1981. This method, known as gigaseal, provided a higher signal-to-noise ratio and enabled the recording of very minute currents. Since its inception, patch clamp technology gained widespread acceptance; currently, automated patch clamps are available, allowing for the simultaneous recording of several single ion channels. This means that the patch clamp represents the very first generation of brain interfaces.

The second-generation neural interfaces made it possible to record and stimulate many neuronal channels in vivo. These tools made it easier to communicate with live individuals using the patch-clamp technique by eliminating the need to prepare samples. Depending on the kind of neural signal being monitored, an appropriate neural electrode is utilized to interface with the brain. Signal processing computers and electrodes are linked via cable. Neural stimulation and signal capture from a live patient are both possible. Traditional electrophysiology, on the other hand, was limited to single neurons with electrodes inserted both within and outside the membrane, and it was primarily concerned with intracellular recording from the peripheral nervous system.

Voltages across the cell membrane are the only thing that can be measured using intracellular recording, although even small changes from the resting potential may be recorded. Signal summations from neighboring neurons may be recorded using electrodes inserted in the extracellular fluid, as in an extracellular recording. While the amplitudes of extracellular neural signal recordings are less than those of intracellular recordings, they cover a wider range of brain processes. Extracellular recordings may be broken down into non-invasive and invasive techniques according on where the electrodes are placed. Electroencephalography is a non-invasive approach, which records electronic brain activities from the scalp’s surface. Electrodes are implanted internally in invasive techniques such as electrocorticography (ECoG), in which they are put on the cerebral cortex top beneath the local field potential (LFP) and the skull, wherein they are normally embedded in the brain tissue (even thouth LFP can also be obtained using the ECoG electrode)

Micro-electrocorticography (ECoG) arrays have been created provide enhanced temporal and spatial resolution compared to conventional ECoG by using tiny electrodes manufactured on flexible substrates. The intrusive method allows for better stimulation efficacy and precision due to a direct engagement with neurons, which in turn leads to higher-frequency signal bands and greater signal-to-noise ratios. Several electrodes are used for signal acquisition purposes. The capture of EEG signals is difficult for non-intrusive extra-cellular records because of the weaker amplitude of signals and the challenge of getting the best contact between the scalp and the electrode, as poor contacts may readily introduce noise. The metals used in traditional EEG wet electrodes include silver chloride, tin, platinum, and gold; gels are placed in elastic caps to boost the signals' quality.

The performance of dry electrodes without gels is equivalent to that of wet electrodes, but they are much more easy to use. Although convenient, dry electrodes have a number of drawbacks in the laboratory, including greaterimpedence of electrode-tissue and a lack of resilience to movement artifacts. In order to combat this issue, active electrodes that have integrated preamplifiers near the electrodes have been developed. Soft conductive fabrics electrodes, injection molded dry electrodes, flexible metal-coated polymer bristles, and polymer foam electrodes are just a few examples of the novel materials and design structures being used in modern EEG electrodes. There are now established norms for where electrodes should be placed, with the number having increased from 11 in the early years to 300 in the present.

Microwires fabricated from tungsten, iridium/platinum, stainless steel, and insulated biocompatible materials are often employed for penetrating electrodes. Enhanced spike sorting performance and more mechanical stability are achieved by bundles of four microwires, called as tetrode. A neural input-output bus (NIOB) to interrelate with approximately 1,000,000 neurons using densely packaged microwires is currently being developed under a DARPA-funded effort. Signal attenuation, cross-channel interference, and interference all pose problems for this method. Instead, needle-shaped silicon micro-electrodes may be used to facilitate multi-site recording. Nevertheless, the recording signal might be weakened if the hard probes irritate or injure the tissue. Polymer electrodes that are flexible enough to penetrate the body are preferable for long-term implants.

Nevertheless, the bendability of the electrodes makes insertion more challenging. For efficient insertion of polymer electrodes, a robotic method has also been introduced. Carbon fiber electrodes with cross sections of several micrometers are one method of minimizing the electrode footprint and hence the tissue response. Carbon fiber arrays with a high packing density have also been created for use in tried-and-true insertion techniques. While microwires were formerly often utilized in peripheral nervous system research, the damage they produce has led to their decreased use in recent years. Intra-fascicular electrodes that are thin and flexible are another option; these are the transverse intra-fascicular multi-channel electrodes (TIME) and the longitudally intra-fascicular electrodes (LIFE). Intra-fascicular electrodes as prosthetic solutions have been shown to have a bright future in experiments.

An arrangement of pores in a sieve electrode (also called a regeneration electrode) allows severed nerves to regrow their axons. Through the perforations and into the distal end, the axons are kept in place by the guiding tube. By making contact with surrounding conductor at the holes, axons open the door to recording and stimulating brain signals. Cuff electrodes, conspicuous non-penetrating peripheral electrodes, are often used in the investigation of brain circuits. Electrodes made of metal are embedded in the silicone and make touch with the nerve from the inside. More spatial embedment, enhanced biocompatibility, and increased long-term stability compared to traditional electrodes are being produced using novel electrodes, such as those reliant on meshes, multi-functional flexible polymer fibres and organic materials.

III. TYPES OF NEURAL STIMULATION

By orienting charges to the neurons, electrical stimulation may alter the functioning of the nervous system. It is possible to represent the electrode-tissue interfaces as parallel-linked double-layered capacitor with a voltage source in series of the resistor. In spite of the fact that we still do not completely understand the theory behind brain stimulation, scientists have utilized it extensively to examine how networks of neurons respond to various stimulation patterns by measuring the activity of individual neurons. Neurological illnesses including epilepsy, Parkinson's disease, and chronic pain have all benefited from its usage in the clinic.

While recording a brain signal, the quality may be degraded by a variety of factors, including the red lines representing typical interior 1/f and current noise from the electrical circuitry themselves and exterior power-line intrusion. The amplitude of an extracellular action potential (AP) is typically less than that of an intracellular action potential; however this difference may be influenced by the recording technique and the location of the neuron relative to the electrode. The power spectral density (PSD) of thermal noise is very nearly the same over the whole frequency spectrum, and its value is around a few microvolts (μV). In 1/f noise, the power spectral density (PSD) decreases as f increases. It is also possible for the front-ends of the neural recorders to be contaminated by noise from the 50/60 Hz powerlines.Based on the application, stimulations could be employed to various areas of the nervous system.

Transcranial electrical stimulation

The current level of telecommunications engineering and science is highly complex. The tES applications within behavioural process dissection, in the analysis of brain system via causal disruptions, and in the focussed therapy of narrower networks of neurological illnesses have been motivated by initial in vitro and in vivo human and animal electrophysiological investigations. There has been a lot of buzz about this body of work, and as a result, many people have come up with different ways to apply it. Some examples include trying to improve sporting abilities, motor skills, and cognitive functions, and using it to treat conditions as diverse as addiction, memory defects, cognitive decline, aphasia, epilepsy, dystonia, migraine, schizophrenia, Parkinson's disease, learning difficulty, pain, stroke, dyscalculia, depression, dyslexia, and autism. In most cases, there is a lack of substantial data and sound mechanical justifications for these claims. Concerns concerning its repeatability, effectual sizes, and reliability have arisen in response to the widespread publicity surrounding the use of tES. Despite the widespread curiosity in transcranial electrical stimulation (tES), important concerns about the method's efficacy, safety, and repeatability, as well as the reasons for its widespread use, remain unanswered. We describe methods for developing tES applications that are more trustworthy and grounded, and we address significant problems in the ongoing discussion.

Spinal cord stimulation

A needle is inserted into the back near the spinal cord, and a device that emits the electrical impulses is implanted there. The pulse generator is inserted into the upper buttock via a tiny incision. The patient has control over the strength of the signals and can switch the current on and off. A pleasant tingling feeling has been reported from some devices, while others have no such effect. Newer devices may affect the perception of pain by shifting the proportion of spinal cord cells that transmit the experience. There are a number of different spinal cord stimulation systems on the market. The most popular types of units are those that are completely surgically implanted and powered by a pulse generator. These days, most gadgets include a pulse generator that can be charged wirelessly via the skin, and that's what makes them so convenient. Some completely implanted pulse generators do not need to be recharged, but they have a lower lifespan and must be replaced more often. Antenna, transmitter, and receiver are also part of a system that uses radio waves to operate. The receiver in these systems is implanted inside the body, while the antenna and transmitter are carried outside. When previous therapies have failed, when surgery is unlikely to assist, or when surgery has failed, spinal cord stimulation may be suggested. But, the gadget is not appropriate for everyone, so it is important to talk to your doctor before using it.

Deep brain stimulation

For the diagnosis of movement disorders such as essential tremor, Parkinson's diseases, and dystonia, including conditions such as epilepsy, and obsessive-compulsive disorder (OCD), deep brain stimulation (DBS) refers to a neurosurgical process integrating the placements of a clinical instrument known as a neuro-stimulator, which transmits electrical impulses via an implanted electrode, to a particular target within the brain. Direct brain stimulation (DBS) modifies brain activity under conscious control, although its basic principles and processes are not well understood. Since 1997, DBS has been recognized by the FDA as an effective therapy for essential tremor and PD. DBS was first licensed in 2003 for dystonia, then in 2009 for OCD, and most recently in 2018 for epilepsy.

Many affective illnesses, including severe depression, have been the focus of DBS clinical studies as a possible therapy for chronic pain. This kind of neurosurgery is unusual in that it permits blinded research. Some of the Parkinson's disease symptoms, which medicine alone cannot treat may be managed by deep brain stimulation (DBS). High-frequency (> 100 Hz) stimulation of the internal pallidum, subthalamic nucleus (STN), and ventrolateral thalamus is used to treat PD, with the goal of simulating the clinical symptoms of lesioning. Patients with PD whose motor fluctuations and tremor are not sufficiently managed by medications, or who are medication's intolerant, are good candidates for this procedure. Patients with significant neuropsychiatric disorders are not good candidates. In PD, neural stimulators have been used to treat four various parts of the brain system. These regions include the thalamus, subthalamic nucleus, globuspallidus internus, and pedunculopontine nucleus.

Nonetheless, the subthalamic nucleus, and globuspallidus internecine the usual targets of DBS procedures. (i) Deep brain stimulation (DBS) within the internalized globuspallidus decreases dyskinesias, or involuntary trembling motions. Better symptom management is achieved because the patient is able to take the recommended dosage of medication (particularly levodopa). Parkinson's disease symptoms may be alleviated by direct stimulation of the subthalamic nucleus (ii). This allows for a reduced dosage of anti-parkinsonian drugs. Freezing of gait may respond to deep brain stimulation of the PPN, whereas tremor may respond to DBS of the thalamus. These targets are seldom used in practice.

DBS target selection is a multi-step procedure that requires careful consideration. The goal is chosen based on a variety of clinical factors, including as the patient's current levodopa dosage, the severity of their symptoms, the effectiveness and side effects of their current drugs, and the presence or absence of any coexisting conditions. For instance, DBS of subthalamic nucleus is not recommended for people with untreated depression since it may make their condition worse. In terms of motor score assessments, DBS is often linked with a 30–60% improvement. Motor fluctuations, which are characteristic of Parkinson's disease, are not totally controlled by DBS since it is supplied continually and with set parameters. As a result, the notion of adaptive Deep Brain Stimulation (aDBS) has emerged in recent years as a kind of DBS that may automatically adjust stimulation settings based on the patient's level of parkinsonian symptomatology. Clinical adoption of aDBS devices is being studied at present.

Vagus nerve stimulation

The vagus nerve (VN), which has its origin in the medulla, has a wider range of functions than any other cranial nerve. As the primary parasympathetic system component, it regulates emotional states, digestive processes, the immune system, and cardiovascular performance. The vagus nerve has negative chronotropic (heart rate lowering), dromotropic (atrioventricular conduction slowing), and inotropic (decreased ventricular contractility) effects on the heart, as expected by its anatomical distribution. The diameter, number of fasciae, and organization of fibrous tissue in the human vagus nerve are all comparable to those in the pig. Vagal nerve modulationscould play a crucial role in future therapeutic trial, as shown by these pig findings. The promise of targeted electrical neuromodulation with low side effects and greater organ selectivity has been bolstered by the discovery of function-specific (organotopic) organizations in the cervical vagus nerve. Diseases of the heart, such as heart failure, benefit greatly from these effects. Myocardial infarction (MI), atrial fibrillation (AF), and cardiac arrest are among disorders for which VNShas being explored as a potential treatment approach. The auricular branch of the vagus nerve is stimulated to send neural signals to the medulla oblongata at the brainstem (reflex center), and then to the heart through efferent vagal fibers. Cymbal concha tVNS is an alternate access point for the vagusnerve. This strategy has the greatest promise, since it reduces the detrimental effects of arrhythmias and heart failure on the myocardium. It's also the most effective therapeutically relevant sVNS method.

Transcranial magnetic stimulation

The symptoms of severe depression may be alleviated with transcranial magnetic stimulation (TMS), an approach in which magnetic fields are used to activate nerve cells in the brain. Since no incisions or other surgical techniques are required, we refer to this as a "noninvasive" method. While TMS has been approved by the FDA in the United States, it is seldom utilized as a first line of therapy for depression. When other methods of therapy have failed, the FDA has also authorized TMS for the treatment of obsessive-compulsive disorder (OCD), migraines, and smoking cessation. TMS's efficacy in treating a variety of conditions, including epilepsy, is still being investigated. Repetitive transcranial magnetic stimulation (rTMS) is a therapy for depression, OCD, and smoking cessation that includes the delivery of several magnetic pulses. An electromagnetic coil is put on the scalp during rTMS treatment for depression. The nerve cells in the part of your brain responsible for regulating your mood and combating depression are stimulated by magnetic pulses delivered by this coil. It may stimulate parts of the brain that are dormant or underactive when someone is depressed.

Deep transcranial magnetic stimulation (or "deep TMS") is another title for this treatment. The coil utilized is what differentiates rTMS from deep TMS. Unlike rTMS, the deep TMS coil may reach more cerebral layers and activate a greater region of the brain. When used to treat OCD or for smoking cessation, deep TMS coils have received FDA approval. TMS seems to impact brain function, although the biological mechanisms behind this are not well known. The effects on mood and despair appear to be reduced or eliminated. TMS may be executed in several methods. When professionals gain more knowledge, they may revise their procedures.

Different kinds of electrodes need a unique electronic multichannel interface; hence several workstations have been designed to accommodate this need. In order to digitize signals, analyze signals, and regulate stimulation, electrodes (described above) are connected to the workstations. One of the most ubiquitous tools in neuroscience laboratories is the workstation, which has greatly facilitated scientific progress. Nevertheless, its cumbersome size disqualifies it from participation in some investigations, such as those involving freely moving participants or those requiring long-term, continuous recording. We need more compact systems with the same or better performance.

IV. WEARABLE/IMPLANTABLE NEURAL INTERFACE DEVICES

Devices that may be worn or implanted have come a long way in the last several decades, showing promise for a variety of individualized health monitoring and therapeutic uses. Wearable and implantable devices for medical purposes are the primary emphasis of this special issue, which also examines electronic and functional materials; sensing capabilities and technologies, and associated energy remedies. We have compiled 17 reviews, 4 research pieces, and 1 viewpoint that are relevant to this field and adequately address the breadth and complexity of the themes at hand.

Nanomaterials are a class of functional materials with unusual features, including the ability to seamlessly integrate into soft, malleable organs and tissues or/and to establish new interfaces for therapeutic and sensing purposes. In order to create soft, bioresorbable devices, Długosz et al. [4]provide a comprehensive overview of the latest developments and advancements in a wide range of additive printing methods, and inorganic and organic nanomaterials. Merits in near interfaces, degradability, biocompatibility, and low impedance in sensing are only few,regarding the benefits of nanomaterials such as nanoparticles, nanofibers, nanomembranes, and hydrogels. Also included are the many printing processes used in the production of implanted devices, including inkjet printing, screen printing, laser sintering, and aerosol jet printing.

Elastomers and polymers are useful for building soft and bio-integrated electronics because of theirprocessability, deformability, and low moduli that allow for conformal contacts with curvilinear and soft biological tissues. Prameswati et al. [5] present a review of the many types of elastomers used to construct soft and bio-integrated electronics, including those that are conductive, semiconducting, sticky, and self-healing. Conjugated polymers, such as semiconducting polymers and conducting polymers have made significant strides in recent years, and Liu et al. [6]provide a concise summary of this development and the design considerations for incorporating them into a wide range of devices of implantable neural interfaces. When it comes to capturing electrophysiological signals, soft electrodes are among major devices that may be used in either a non-invasive or invasive fashion. An array of wire, mesh, and film-based soft, flexible electrodes for use in wearables and implants are discussed by Eskandarian, Al-Rasheed, Paul Ilogon, Toossi, and Naguib

[7]. In this article, Lyu, Gong, Yin, Dyson, and Cheng [8] present an overview of the design techniques for future soft healthcare devices, including their use of soft materials and deformable microstructures. The authors also discuss the recent development of soft, wearable medical devices for continual tracking of biological, chemical, electrical and physical data.

For the development of bio-interfaced electronics, liquid metals are an attractive choice due to their inherent stretchability and high conductivity. The features and processing methods of soft wearable electronics based on liquid metal are reviewed by Nie et al. [9]. Challenges and future possibilities are examined, along with some concrete examples of use in the fields of biosensors, soft interconnects, and brain interfaces. The use of biological materials in the creation of wearable electronics is also very desirable due to these materials' abundance, sustainability, biocompatibility, and biodegradability. Based on different sensing approaches such as capacitive, piezoresistive, triboelectric, and piezoelectric effects, Kim, Song, Park, and Yun [10] provide a summary of the biomaterials and architectures utilized in implantable pressure sensors. In view of the rising need for short-term biomedical implants, Lorenzo Ruiz [11]discuss the progress achieved in developing implantable devices integrated with metal alloys and bioresorbable metals for therapeutic and diagnostic purposes.

Several studies in this issue report on new conductive materials and technologies that may be used to create high-fidelity, durable, and wearable soft sensors. Poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) composite materials with biocompatible IL (ionic liquid), cholinium lactate, have been developed by Wood, Jarratt, Barker, and Brown [12] to create mm pitch-size surface electromyography arrays, which will allow quality forearm activity and motion spatiotemporal recordings. Conductor eHelix is described by Zhao et al. [13] as a combination of wires of helical copper wires and soft elastomers, and it is very stretchy and dependable, with deformation-insensitive and robust electrical conductivity. The eHelix has been put to good use and its applications have been verified in a variety of gadgets, such as monitor of the heart rate, tactile detecting glove.

Wearable and implanted sensors and electronics have benefited from several recent developments in materials and technologies, but really advanced sensing and progressive surveillance have to be sustainable, battery-free, or bio-compatible clinical equipment. A diversity of non-battery sources of energy, such as mechanical energy, electromagnetic energy, biofuels, thermoelectricity, wireless power transmission, and triboelectricity, are summarized by Chaleekure, Boonraksa, Junhuathon, and Marungsri [14], for use inbatteryless, wearable devices. Implantable devices, unlike wearables, place a greater emphasis on the power solution and provide more challenges. Battery and supercapacitor storage; biofuel cell and triboelectric and piezoelectric harvesters; biopotentialand thermoelectric power generators; and inductive coupling, ultrasound, and photovoltaic wireless power transfer devices are all described by Irwanto, Nugraha, Hussin, and Nisja [15].

In example, there are several implanted devices that benefit from wireless power transmission. Inductive coupling, RF, mid-field, magnetoelectrics, light, and ultrasonic are only some of the frequently documented wireless power transmission technologies that have been studied in relation to implants. Ding, Koulouridis, and Pichon [16]analyze all six of these methods. Power, downsizing, depth, alignment tolerance, transmitter distance, and safety are just a few of the key tradeoffs or design concerns that are compared across various technologies. To address the difficulties caused by the limitation and need of in vivo operation, McRae [17] compile the most current developments in RF-centric telemetry and wireless power transmissions (for physiological collection of data) for wearable bioelectronics in a review paper. As a potential wireless power transmission method, Maniar and Singhi [18]assess the current ultra-specific implants. There is a summary of the various piezoelectric nanomaterials and harvester devices, including lead-free inorganic, organic polymers, and lead-based inorganic, along with a presentation of performance measurements and examples of their practical uses.

Wearable, soft, and flexible sensors have several applications, one of the most important being their ability to continually monitor physiological data that are highly correlated with an individual's health. Monitoring heart rate is one important use to reduce the risk of cardiovascular disease and related deaths. Electrocardiography, blood pressure, heart rate,blood glucose, and blood oxygen saturation are only few of the cardiovascular indicators that may be monitored in real time by flexible wearable sensors, which are discussed in detail by Manjunatha, Shwetha, Athreya, Kumar, and Kamath [19]. Provided the significance of diastolic and systolic monitoring of the blood pressure in directing medial decision-making in the pediatric intensive care unit, Dalal, Gaydos, Gillespie, Calamaro, and Basu [20]show how to use soft skin-interface implantable devices (optimized by critical selection of mechanical designs and materials) to monitor diastolic and systolic blood pressure wirelessly and continuously on pediatric patients. Several indicators, such as heart rate, body temperature, and even muscle and brain activity, may be tracked using wearable sensors. Li, Lee, Lim, and Lee [21]present a flexible, wearable system that combines a $ZnIn_2S_4$nanosheet-centric humidity sensors and carbon nanotudes/$Sn0_2$ sensors for temperature. This system has been effectively assessed on a healthy volunteer to research on the thermo-regulatory feedback to cold exercises and stimulations, with the goal of developing a method for early forecasts of thermoregulation disorders [26],[27],[28].

The continual surveillance of molecules provides a big potential and gap in the current state of health monitoring, which focuses mostly on monitoring health-related physical metrics using commercially accessible wearable devices. Microneedles have been shown to be an efficient and minimally invasive way to gain access to interstitial fluid, which can then be used to monitor metabolites, electrolytes, and drugs in real time. Yang, Liu, Fu, and Song [22]discuss recent advances, emerging trends, and unmet challenges in this field. Therapeutics might be tailored in real time based on the biomarker information gleaned through continuous monitoring of physiological fluids, therefore enabling customized treatment. Closed-loop diabetic treatment, in which medicine distribution is adjustable in response to monitoring blood glucose levels, is a good illustration of this principle in action. Yoo and Kim [23] outline the latest developments in implanted insulin delivery systems and continuous glucose monitors for greater individualization of diabetes care, with an emphasis on materials and design.

Extensive human research is required to successfully translate existing proof-of-concept implantable and wearable devices. To examine the implantable prototypes from an analytical point of view, Vanderhout et al. [24]offer pertinent ethical considerations on many elements of preliminary human research (such as validity, and reliability, subject selection, risk evaluation, data security and privacy, and informed permission) in a perspective paper. When it comes to analyzing and processing the massive amounts of physiological data produced by implantable sensors in human research, machine learning is a viable technique. In this article, Huang and Barnard [25]provide a comprehensive review of the techniques of machine learning utilized in data processing for public health and medical practice applications, as well as a summary of the various forms of physiological signals and non-invasive biosensors gathered from the human body. Wearable and implantable technologies have the potential to be widely used in clinical diagnosis and daily medical monitoring for different health disorders if additional technology advancements are made and human validation is undertaken ethically.

We now refer to these wearable/implantable devices as the brain interface third generation since they are small, cable-free, and feature bespoke printed circuit board (PCB) and application-specific integrated circuits (ASICs) level integration. There are different design concerns in the establishment of smaller, wearable/implantable neural interfaces. Wireless control signal transmission and dataset are applied using either bespoke designs or commercial solutions, and signal processing could be attained on different computers, a general-purpose ASIC or microcontroller. Some of these include dependability (in terms of data link/loadconstancy, signal recording quality, physical electrode link-ability, and the signal processing accuracy) and safety (in terms of tissue harm caused by wearable electrodes and the recording and stimulation electronics). Modifiable parameters include amplification strength, bandwidth, sample rate, channel selection, and stimulation settings, and both recording and stimulation may be done on the go (the miniatureization of the entire model's size is significant, mostly for study on freely-shifting subjects, and smaller domain electrical devices and compacted integration techniques are therefore required.).

The application of custom-based models has the capacity to fundamentally reduce power and size consumption (provided a constraint of the model size, a minimal consumption of power will enhance the lifespan of battery for long-term research, including the limiting tissues damage due to dissipated heats). Signal processing/feature extraction, a closed-loop control modules, a brain stimulation module, and an acquisition module are all components that may be added. Lower input-based noise, effective dynamic range, high linearity, high input impedance, higher power-supply rejection ratio (PSRR), and higher common-mode rejection ration (CMRR) are all fundamental for neural signal acquisition front-end. The NEF (noise efficiency factor) is a widely-acknowledged figure of merit; it is the resulting noise from neuronal acquisition front-end amplifiers that the single bipolar transistors with similar bias.

The efficiency of the acquisition front-ends is measured in a number of different ways, including the system efficiency factor (SEF), and power efficiency factor (PEF). In order to mitigate the significant input DC counterbalance and increase the input impedance, the AC-based amplifier is often used in conventional neural acquisition front-ends. The DC-coupled amplifier can cut down on the size of the blocking capacitors, but this might have a negative impact on the CMRR. Recent tendencies either use modulators or time-centric recording front-end, to directly transform the referent signal without amplifiers, hence attaining enough dynamic range that is needed in bidirectional neural interfaces. There are three major forms of stimulators. The stimulators in voltage mode are more efficient in terms of energy consumption and have less complex circuits. The quantity of charge delivered to the tissue is difficult to regulate, however, because of the electrode tissue interface's variable impedance. Stimulators that operate in a current mode are more effective in regulating charges, but they waste more power in the process. High efficiency and precise charge management may be achieved by stimulators operating in the switched-capacitor mode, but this comes at the expense of a significant amount of chip real estate. Electrode tissue interface charge accumulation needs to be halted for biosafety purposes. Stimulation with a biphasic waveform gives more command over charge-balance. Dynamic charge balancing and monitoring approaches are preferred in cutting-edge stimulation designs, despite the fact that symmetrical anodic and cathodic phases may be achieved with careful design.

On-chip feature extraction and neural signal processing

In order to decipher brain activity and subject behavior, several neural signal processing approaches have been created. In this article, we show on-chip implementations of general-purpose neural signal processing algorithms and the regulation of a closed-loop neural interface. Processing inputs and extracting discriminative features is a crucial part of a closed-loop neural interface. While standard microcontrollers and digital signal processors (DSPs) may be modified for use in the medical field, they are not as power-efficient as NPUs built specifically for the brain. There are three main functions of on-chip signal processing models formulated for neural interfaces: feature extraction from brain signals, data compression before transmission, and closed-loop control-focused modules. There has been extensive use of methods for extracting features from neural signals, such as narrow power in narrow frequency spectrum, AP spikes, and characteristics in the frequency-duration wavelet domains, phase synchrony, and entropy.

High-level characteristics are extracted directly in certain projects, such as those that seek to identify the start of neurological disorders, to classify the stages of sleep, and to decode the goals of a given movement. The system's capabilities may be expanded beyond data gathering to information acquisition with the use of online neural signal feature extraction prior to data transmission. Neuronal signals associated with a particular mental state may be localized to a limited frequency band, particularly at the low end of the spectrum. The most prevalent frequency sub-bands for brain signals are as follows: theta, 3-8 Hz; delta, 0.5-3 Hz; alpha, 8-12 Hz; gamma, 38-100 Hz; beta, 12-38 Hz. The design of the energy extraction circuit is significantly complicated by this. Analog and digital neural energy detectors and others have been developed. Changing the filter coefficient registers in a digital implementation was all it took to fine-tune the energy band.

Band tuning is more challenging with an analogue version, but power consumption is reduced. Either domain-time amplitude characteristics or energy-domain characteristics may be used for on-chip single AP spike identification. Due to their ease of use, dual-threshold domain-time approaches, either with adaptive or fixed threshold, have become famous for AP spike identification. Approaches in the energy spectrum [e.g., non-linear energy operator (NEO)] are more durable. There have been reports of ASICs for AP detection that use novel algorithms like the exponential component-polynomial component (EC-PC) engines. The minimum and maximum spike amplitude, derivatives of spikes, and spike widths are all useful AP characteristics, which can be retrieved during a single AP detection. Online spike sorting has found widespread use. K-means clustering, and Principal component analysis (PCA) are two methods that attempt to strike a balance between the computational complexity, energy consumption, and storage needs of their respective algorithms.

As compressed sensing only requires a one-time encoding, it has found widespread application in implantable/wearable neural interfaces for real-time data compression. Selecting which bits of data to transfer can also slow things down. When associated neural activity (for example, AP spikes) are identified, data could be transmitted only when necessary, or only retrieved neural characteristics might be conveyed in place of raw data. This is made possible by on-chip signal processing. Modules that are focused on closed-loop control are crucial in many practical contexts. PID, detected features, and AP spikes, can all be used to initiate stimulations. The analogue stimulating backend, and analogue recording front-end must be integrated into the same system, if not on the same chip, in order to accomplish closed-loop control. Stimulation artifacts occur when a powerful stimulation signal overwhelms the amplifier in the recording front end.

Closed-loop system design becomes significantly more difficult when trying to mitigate the stimulation artefact's negative effects. There have been numerous attempts to find a remedy. One such method is the blanking technique, which involves pausing the recording for a few time after the stimulator has been activated; this is a straightforward approach, but it results in undesirable gaps in the data. Instead, saturation prevention or quick recovery may be used in the analogue domain to weaken the artifact. Digital signal processing, such as artifact subtraction or signal interpolation, may also be used to mitigate this impact. None of these methodologies, however, have yielded a satisfactory answer to the problem of artifacts; therefore co-designing them may be useful in future studies.

Applications of wearable/implantable neural interface

Several neurological illnesses may be successfully treated with neural stimulation. The Medtronic Summit RC+S system, the CorTec Brain Exchange system, and the Neuropace RNS system, are all examples of closed-loop neuromodulation devices designed for regular clinical usage. The progress of integrated circuits aids the enhancement of wearable neural interface instruments. The IMEC EEG headset is just one example of several non-invasive EEG medical monitors on the marketplace. Multi-modal recordings on front-end integration on a single chip are another current direction. This may also assist thehybrid neural interface that integrates multiple brain signals to expose more data to boost the neural interface performance. There have also been reports of the use of small neural interfaces in freely-mobile animals for neuroscience study, with the goal of elucidating the relationship between behavior and brain activity. Invasive or non-invasive brain signal recordings may be used to decipher motor intention. Wheelchair users may be able to converse with others and control their own motions via neural interfaces.

The miniaturization of electronic gadgets will assist bring neural interface prosthetic arms and hands out of the lab and into clinical practice. Cochlear implants have employed neural stimulation for decades; retinal stimulation prosthesis may have a similar effect on one's vision. The effectiveness of neural inter-faces in the treatment of neurological disorders, such as stroke recovery, has been shown in several clinical trials. Paralyzed persons with spinal cord injuries may one day be able to regain movement and sensation via experimental procedures that have shown promise in both nonhuman primates and humans. By activating the central nervous system, and the peripheral nervous model, electronic skinmay assist restore tactile sensing. There are a number of obstacles that must be overcome before implantable/wearable neural interfaces may be brought to market. To begin, there is not enough medical knowledge about the nervous system's inner workings. From a circuits and systems perspective, power efficiency must be enhanced. From a material and device standpoint, the biosafety of long-term implantations is unclear. Tissue encapsulation still poses a problem, as it might reduce the quality of recorded data and increase power usage due to signal attenuation.

V. CONCLUSION

Fourth-generation neural interfaces increase the density of contacts thanks to their high level of integration. With the development of these fourth-generation brain interfaces, it is now possible to implant many devices into a single human being. Another possibility is to leverage wireless connections amongst the various neural interface devices to create a synthetic network that mimics the brain's neural network. Nevertheless, these advancements raise additional problems, such as how to effectively power up implantable devices, maintain the confidentiality of the data, and communicate huge amounts of data (up to someGbps) between devices and between living tissues, and devices. Power might be saved by reducing the transceiver's burden with the use of on-chip signal processing. Transmission would be limited to data meeting specified criteria or to neural markers that have been retrieved. The neural interfaces might be managed on the chip without the need for constant communication with external devices by use of closed-loop control modules. As a result, the rate at which brain activity is converted into machine language will increase. An efficient artificial neural sensing capacity may become possible because to improvements in both the speed and accuracy with which neural signals can be acquired and the intensity with which they can be stimulated.

What is the optimum compromise between effectiveness and security, and how much decision-making ability and intelligence should be provided to the gadget, are ethical questions that arise from this. Here, we have mostly discussed electrical neural interfaces, although they are far from the only methods of influencing brain activity. To date, no electronically embedded devices have been documented, despite the fact that ultrasound may be guided activate and non-invasively the nervous model on a millimeter scale. In place of electrical currents, light may be employed to stimulate nerve cells. In 2005, optogenetics was first used to regulate individual ion channels. The ability to choose which neurons to stimulate is made possible by the expression of light-activated proteins, which respond to certain wavelengths of light. Nevertheless, this calls for intricate pre-processing of the cells using chemical and biological methods, which is not always safe for human patients. Nevertheless, new studies show that wireless optogenetics-based brain stimulation may be possible even without waveguides. A new generation of brain-machine interfaces may be possible by the integration of needle-shaped electronic neural interfaces with fiber-based optical neural interfaces.

Data Availability
No data was used to support this study.

Conflicts of Interests
The author(s) declare(s) that they have no conflicts of interest.

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