

Advanced Architectures and Materials of Functional Devices for Neural Interfaces

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Abstract. Architectures and materials of functional devices at neural interfaces have advanced quickly over the past few decades. Direct implant into the brain is required for conventional invasive procedures, which present a risk of inflammation due to its open craniotomy. New technologies were pushed to be developed to avoid inflammations, as the four most iconic architectures that can be minimally invasive: filamentary probes, conformal sheets, open-mesh networks, and distributed material elements appeared in researchers' vision to record and modulate neural activities. This review unveils their mechanisms, functions, and effects respectively. Additionally, this discussion covers the most current findings regarding the roles played by these four architectures, including their structural designs for neural interfaces and their potential future applications.

Keywords: Filamentary probes, Conformal sheets, Open mesh networks, Distributed material.

1. Introduction

Implantable neural devices are vital to record and modulate complicated nervous activities. There has been a surge in research, innovation, and potential uses for this episode of creations. Various interfaces in different shapes must maintain stability over the prolonged periods involved in memory formation and better cooperate with plastic changes within neural systems. As of today, rigid body implants pose a significant risk due to an in-body immune system response. Scar tissue produced by such an effect prevents either an electric shock from the device controller or the data collection from the implant probe/sheets from working correctly. Clinical researchers have also adopted knowledge from fundamental neuroscience studies to create innovative neural interfaces with advanced-level materials that can be used to improve current clinical implants. Numerous important research perspectives into the function of the central and peripheral nervous systems have been directly attributed to advancements in neural interface innovations and related experimental strategies. All of these are to improve patient care and eliminate post-implant adverse effects.

Because of probes' technological maturity and commercial availability, the most widely used technologies employ various forms of micro-manufactured pins and probes, where electronic recording and stimulation take place via regular metal electrodes and physical penetration. Ways of stimulating neurons [1-6] also are of paramount importance and include several types of stimulation methods that have been proposed. These methods covered traditional electrical stimulus, optical stimulus, and finally, thermal simulations. Mechanically, materials and frameworks must also encourage designs that can expand to high-resolution, wide ranges of measurement/stimulation locations and retain great biological interfaces over extended periods. Carbon fiber needles, in particular, have been used in such implants [1]. The structure requirement necessitates not only simple production but also the preservation of soft physical properties and curvilinear geometries similar to those of neural tissues, which mitigates the immune response.

Aside from the majority of common probes, optoelectronic and bioelectronic devices made of fully functional thin-film membranes [7-9] and open network meshes [8-10] capable of powerful functional integration with existing technologies are now attracting researchers' attention. Direct contact between tissue and electronics is possible by massive arrays of active components, some of which

have thousands of independent channels. Demonstrations of secure, long-term operation in living, behaving animals are among the most notable in recent research and developments [7].

Distributed material elements, including acoustic, electromagnetic induction, and optogenetics. As electromagnetic induction, and optogenetics are the two dominating technologies, we only discuss them as our topics.

Optogenetics is a special technology, which provides a new direction for developing diversified gene-level operation tools for advanced biomedical applications. As a powerful neuromodulation tool, optogenetics of up-conversion nanoparticles (UCNPs) is used. UCNPs as the main representative of optogenetics, have received great attention in the past few decades.

Magnetic nanoparticles (MNPs) are the main representative of wireless magnetothermal. The fast-dissipating magnetothermal cycle causes the least thermal damage to the surrounding tissues, and it will shrink after other treatments. This result has been proved by researchers several years ago.

The findings of the most recent innovation proposals in the field are outlined in the following sections, with an emphasis on those that could lay crucial groundwork for advancement in the future. The review begins with an introduction of various architectures that interact with the nervous system. A variety of neural interface architectures, such as filamentary probes, conformal sheets, open-mesh networks, and finally, distributed material elements, are being developed as a result of technological innovations and advancements, particularly in material science. These sophisticated platforms have applications that went beyond the realm of neuroscience research, and they have been put in applications, including pharmacological and surgical implants used to treat physical or mental diseases. The creation of innovative components for massive platforms with high densities that can measure and control the activity across large neural systems to single-neuron and even across big, three-dimensional neuro space is what will shape the next generation of neural interfaces.

As a series of collections regarding neural devices are considered, this review provides a general foundation for thinking about architecture advancements in such neural implant systems. Fruitful studies in such areas could lay the robust groundwork for succeeding iterations of filamentary probes, conformal sheets, open-mesh networks, and distributed material elements with a long-life span and high-performance operation with significant help in laboratory preclinical studies or even nurture the potential for commercialization into clinical use.

2. Emerging Architectures and Materials

2.1. Filamentary Probes

Numerous ongoing research projects related to the field of neural interface technology concentrate on neuromodulation probing methods that are capable of more than just generating electrical impulses. As narrow geometries produce low bending stiffnesses and subsequent compliance to the surrounding biology, filamentary architectures make it easier to implant materials into specific neural tissue. Arrays of tungsten needles, carbon fibers, and platinum (Pt)/iridium (Ir) microwires are effective methods for implantation across huge surfaces and numerous channels in electrical interfaces [1].

Researchers are currently developing and testing ultra-small organic electrical microelectrodes with a subcellular cross-sectional dimension that is flexible and sturdy. They have the required electronic characteristics for brain signal recording and enhanced bioactive properties for influencing intrinsic biochemical mechanisms [4]. Researchers created composites to broaden the microelectrode design spectra for operational specifications, including chronic effectiveness was formerly constrained by existing techniques' inherent size, resilience, and electronic trade-offs. So, what we have for today are carbon fibers with a 7 nm diameter mounted onto a PCB with microelectrodes to create the Micro Thread Electrodes, as shown in Fig. 1 [4].

This technology's main breakthrough is the fusion of cutting-edge composites to produce a small organic interface with a size like a traditional silicon neural probe. However, maintaining the flexibility and strength to function alone, the topic of advanced material in neuro applications is still worth researching.

Recent research has shown that precise temperature probe technique control can be used as a substitute for conventional electrical probes. This technique is relevant for treating peripheral neuropathy and neuropathic pain. The underlying principles are temperature-induced adjustments in cellular membranes' capacitance or variations in the conductance of thermosensitive transient receptors [2], both of which lead to ionic transport. The causes of the earlier and later effects are thought to be gradual warming or cooling of the baseline temperature and transient. From what we have discussed above, the optic solution is also somewhat related to thermal effects.

The direct absorption of light and visible light by the targeted tissues or indirect absorption of light and visible light [3] by injected compounds that impact light conversion into thermal energy are some of the most widely investigated methods of delivering thermal energy. Here, the effectiveness of energy conversion affects the lag times between the start of stimulation and neural manipulation. In contrast, response time for heating caused by optical means can be within the scope of milliseconds; those for heating caused by absorbing materials can vary regarding the exact mechanisms. Due to thermal probes' ability to perform neuromodulation with minimum invasiveness, thermal stimulation is one of these recently explored options for matching localization to the size scales of microscopic elements like ion channels and neuron membranes [2].

As a precisely focused version of neuromodulation, the optical probes use photosensitive ion channels or proteins generated in genetically engineered neurons. Optical approaches that don't rely on heating can get around many constraints. Here, under light exposure at specific wavelengths, changes in the structure of opsins, or light-sensitive proteins, take place. Opsin-expressing cells can be stimulated or inhibited by the ionic current flowing across the cell membrane. These processes make high temporal precision possible but are constrained by cellular and single-cell-type accuracy within the illumination volume. Optogenetics treats spinal cord injury, chronic pain, depression, and epilepsy [5] *in vivo*, with evidence from studies in cultured neural networks.

The innovative fiber uses a temporary shuttle made of tungsten wire to give mechanical stability, which is then removed. Stimuli-responsive materials can serve as temporary shuttles' substitutes by providing structural rigidity while implanted and then softening afterward. In one instance, modulus reductions of several orders of magnitude are possible. after implantation attributable to a polymer with a close-body-temperature shift.

The moduli of hydrated fibers are much lower than those of traditional silicon optical fibers. Blue light administration into the mouse hippocampus under stable operation for four weeks [5] is used in animal model demonstrations to activate ChR2-expressing neurons. By taking advantage of constituent materials' swelling, a similar approach can be employed to create filamentary probes with moduli comparable to those of brain tissues. The dehydrated form of the hydrogel is rigid enough for implantation into neural regions, after being exposed to biofluids, swelling and softening occur [8].

2.2. Conformal Sheets

Typically, conformal sheets consist of a soft electrode and a thin elastic layer of the membrane that can connect with peripheral nerves for targeted neuromodulation. Highly conductive hydrogels are first synthesized to achieve the necessary conductance when patterned into a microscale thin-film structure. Next is a stretchy insulation material with Young's modulus calibrated to nerve tissue. After that, the lithographic technique was used to shape the two elastic materials into a multielectrode array. Additionally, studies present its biocompatibility for chronic implantation and hydrodynamic stability. In the *in vivo* experiments (Fig. 2) [6], the framework constructed is shown to efficiently generate electrical pulses with high current density at incredibly low voltages.

Functional thin-film membranes are novel bioelectronic or optoelectronic devices. The level of functional integration offered by these devices is typically very high. Direct tissue and electronic interactions comprise a wide-ranging active component matrix, often with thousands of separate channels. The most significant recent developments include safe, long-term operations in living, moving, and behaving animals, for example, the hippocampus [7]. Conformal sheets minimize immune system responses and tissue damage while supporting device performance characteristics. In

some cases, they are comparable to traditional rigid, planar semiconducting silicon wafer supporting planar electronics, which are the key enabling features of hybrid, integrated platforms. These features include biocompatible constituent materials, those "perfect" structurally compliant frameworks and biofluid boundary coatings.

The critical enabling features of hybrid, integrated platforms are conformal sheets designed to support device performance that, to some extent, are comparable to those of traditional planar electrical components on rigid semiconductor chip panels. Conformal sheets are also designed to elicit a minimal immune response and tissue damage. These features include biocompatible constituent materials, which are "perfect" biofluid barrier coatings, and mechanically compliant configurations. However, conformal sheets face challenges when asked to magnify their sensing capabilities.

There has been progressing in demonstrating the most practical applications of thin active devices in conformal layouts for multiplexed addressing and spatially amplified senses. These conformal layouts solved the problem of connecting electrophysiological interfaces to surfaces and interiors of either heart or brain [6].

Preventing biofluid penetration into and out of active electrical parts is a constant challenge. The escape of current can cause biological harm from electrical leakage into nearby tissues as well as fluid degradation from the corrosive environment of biomaterials.

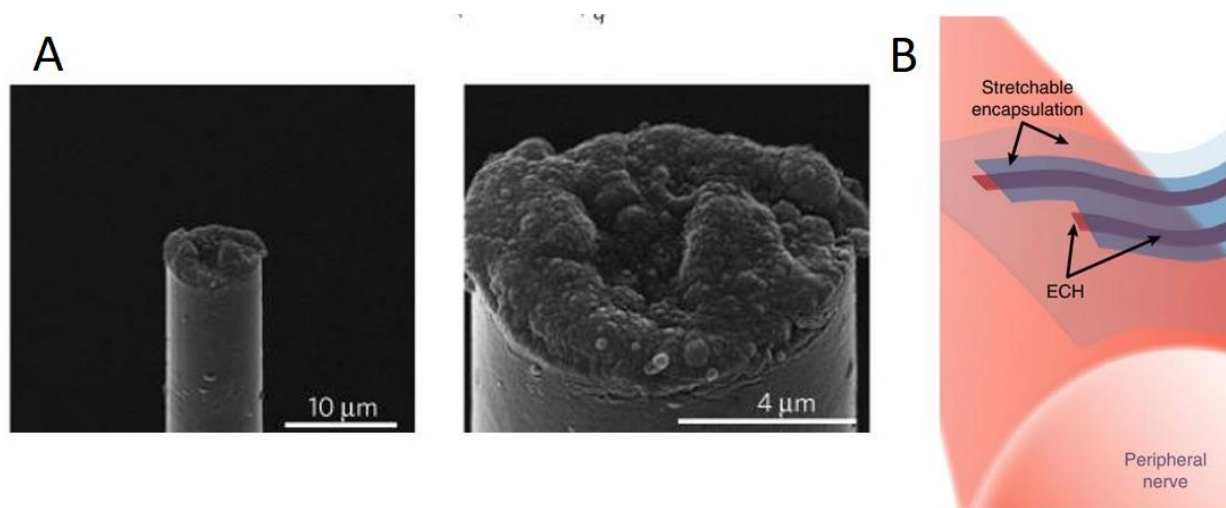


Figure 1. (A) Structure of current filamentary probes under the microscope [4]. (B) demonstration of conformal sheets attached to round neural surfaces [6].

2.3. Open-mesh Networks

An intracranial electrode array, which is used to record and stimulate brain activity, has made great progress in nerve therapy in the past decade. The traditional probe may cause the danger of tissue inflammation, so it is necessary to open the craniotomy directly to implant the conventional probe. Therefore, a minimally invasive method has been developed to avoid brain injury, and an open mesh network appears in scientists' fields of vision, with micron characteristic size as neuron cell body and effective bending stiffness value as dense nerve tissue. It is an open grid network, which has a variety of structures, including stentodes, three-dimensional (3D) electrodes, etc., and is usually used as a grid electronic device.

2.3.1. Stentodes

Stentodes (Fig. 2), a stent-electrode recording array, are worked via complicated procedures.



Figure 2. Schematic of a stent-electrode [11].

Through the capillary needle, the flexible open reticular electronic device was injected into the target brain area in a stereotactic way, with a positioning accuracy of 20 μm . The computerized tomography confirmed the expanded shape along the injection direction after injection. Then, the I–O pads of the open mesh electronic device were connected to the lightweight, flexible flat cable [12].

To maintain the superplastic characteristics of the stent, it is necessary to cross-link and add the installed electrodes along the repeated stent struts. Then, to achieve nonlinear expansion to match the curvature of the target blood vessel, the self-expanding stent enables the electrode array to be compressed during minimally invasive delivery through the catheter. Meanwhile, the electrode and the cortical surface are tightly attached to the blood vessel wall after deployment. We can implant the stent into the exact area via specific catheter technology (online method) and other technologies and then chronically record the activities in particular areas. As for the investigation, measuring the distance from the strut to the lumen in vitro combines the stent into the blood vessel wall using synchrotron X-ray imaging. It evaluates the distance change and impedance in duration [13].

2.3.2. Three-dimensional electrodes

The three-dimensional structure (Fig. 3) of the three-dimensional electrode allows the electrode to fully sample the 3D interconnected tissues of the brain. Recent research shows that the construction of a 3D electrode cube is mainly carried out by creating polyimide catheter arrays 1 mm apart each. A catheter with 3 to 10 bundles of microfilaments of different lengths. The leading microelectrode has a microelectrode made of stainless-steel filaments in each bundle. In the plastic case of 3D printing, the guide tube is fixed, and the miniature screw used to position the microelectrodes is also installed in the case.

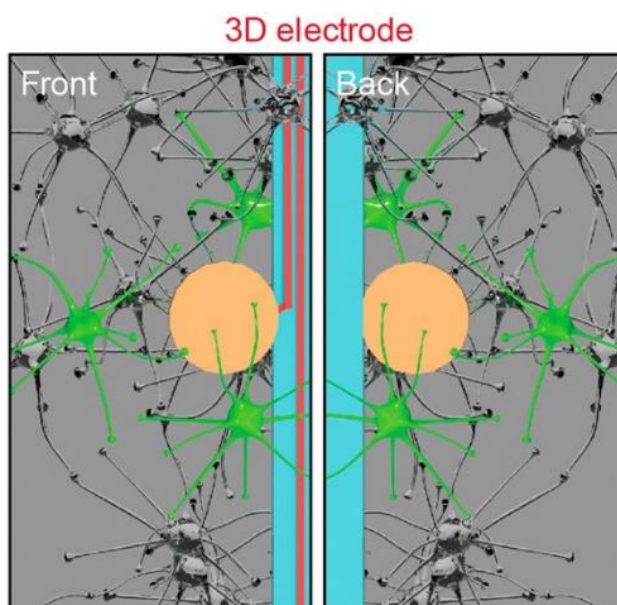


Figure 3. Schematic of two sides of the 3D electrode in the neural tissue [14].

Since three-dimensional electrodes are often used in the implantation process, the catheter array will not penetrate the brain. After a few days, push the micro-toes into the cortex and rotate a set of micro-screws. In one or several catheters, each micro-screw will accommodate the microelectrode. During the operation, microelectrodes were inserted into the cerebral cortex. Although these implants are not as durable as our movable arrays, with the help of fixed arrays, there is minor damage to the cortex. The penetration of a subset of microelectrodes can reduce the depression on the surface of the cortex by using a movable array, preventing multiple microelectrodes from penetrating simultaneously in traditional arrays and silicon probes. In this way, each microelectrode beam is gradually reduced over several days. Entering the cerebral cortex will make microelectrodes more slowly and deeply [15].

2.4. Distributed Material Elements

Distributed material elements include two dominating aspects of optogenetics and magnetic heating and a few acoustic technologies. Fields absorbed and scattered by tissues to a great extent can be used, and a pipeline for deep brain stimulation is what they all need.

Optogenetics' neuromodulation method (Fig. 4) is an optical technique for manipulating biological activities by visible light, which is called to control the functions and activities of neurons when using light. Lanthanide-doped UCNPs are a new candidate for optogenetics applications because they digest limited particles in the near-infrared gap and emit high-energy photons in the visible light spectrum via a nonlinear process [16].

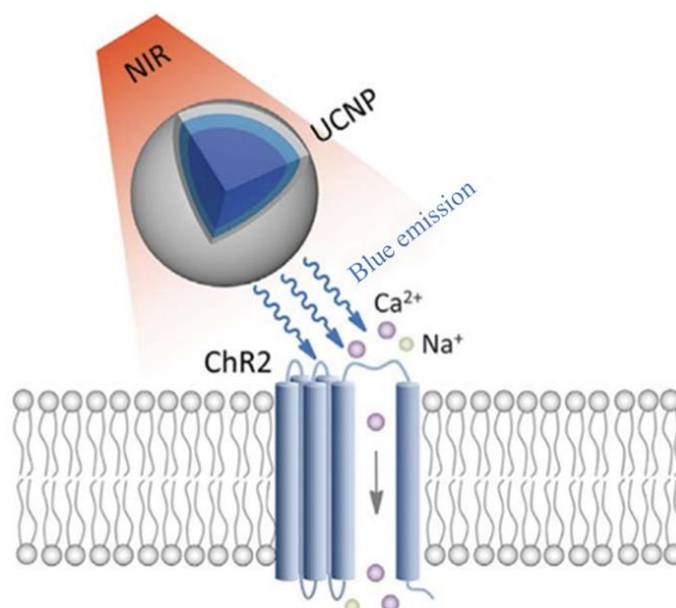


Figure 4. Schematic of Optogenetic Stimulation Mechanism [16].

Low radio frequency can penetrate the human body without significantly attenuating the alternating magnetic field. It differs from acoustic and optical signals, so deep brain areas can transmit signals to magnetic nanoparticles. Oscillating magnetic fields can stimulate biochemical mechanisms, and heat is radiated from moving magnetic nanoparticles through the loss of power. Although MNP heating (Fig. 5), which has been studied for 50 years, is a cell destructive therapy in magnetic hyperthermia, until recently, this effect has been used to control depolarization of cell membranes and gene function in engineering xenografts and invertebrates. In the experiment of targeting MNP to the cell membrane, it takes tens of thousands to thousands of seconds to observe the increase of calcium influx when the synthetic transgene is used in the early stage, which exceeds the temporal dynamics of neuron discharge by several orders of magnitude. Recent studies have shown that the functionalization of MNP and protein induces the internalization of cells and the formation of protein crowns, and the efficiency of in-vivo targeted delivery and heat dispersion may also decrease [17].

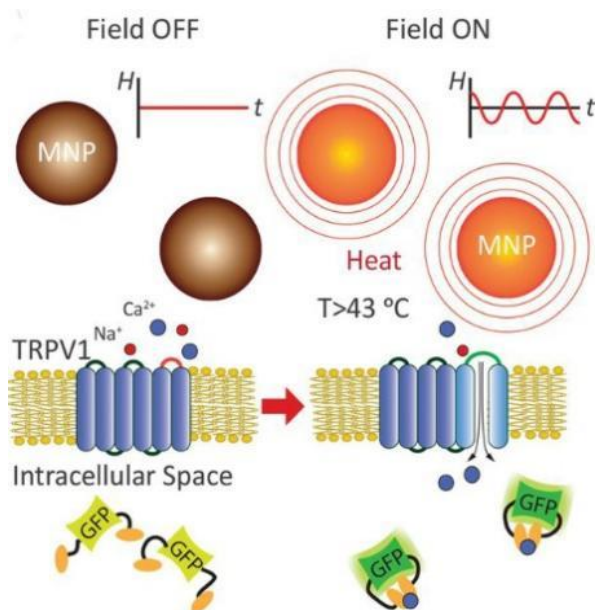


Figure 5. Schematic of Magnetic Stimulation from MNP Heating [17].

3. Discussion

The size and strength restrictions on the polymer technology hampered the probes' ability to integrate with the tissue and reduced their in-vivo longevity. This called for more compact electrode designs that were also strong. The material of choice to fulfill these specifications was carbon. By several orders of magnitude, the carbon core electrodes were more durable and flexible than the silicon probes. Another notable example is the "Neuralink", which transforms filamentary systems into deeply integrated, enormous arrays suited for manufacturing and commercial use [9]. This system provides many electrodes throughout the brain and is ideal for measuring and activating individual neurons.

The most stringent requirement is the call for coverings with micrometer thicknesses and zero water permeability over durations of many decades (patient lifespan). Massive containment housings, such as those used for traditional implants, are ineffective. The advancement of a comprehensive aggregate of substances with active, passive, barrier, and interaction properties continue to this day, as well as corresponding plans in materials processing and assembly, which is the wide central focus in materials science regarding conformal sheets.

Thin, flexible sheets are used in platforms that integrate non-invasively, without penetrating, and conform to the surfaces of neural tissue. The resulting features enhance filamentary probes' capabilities, enabling unrestricted movements of the surrounding soft tissue such as bending, stretching, and twisting. On top of that, having a tremendous geometric conformality to their curved forms, the compliant mechanical qualities are crucial. The main focus areas are the development of large microelectrodes relying on such hydrogels and their inclusion in multipurpose systems built for recording and stimulation. Surfaces made of stimuli-responsive materials enable the opportunity to mold devices to meet the geometrical constraints of tissues without applying force externally.

What has higher consistency is the open reticular network, with stable continuous capturing and stimulation, reproduced from the same single neuron or neural circuit, especially when compared with the traditional brain probe, which usually shows peak shape changes in only a few days to a few weeks. What may not be achieved in a few weeks is the more common case. Because the device works well in separation from the I-O fixed on the skull, especially in terms of mechanism, these findings are related to the comparable bending stiffness values of reticular electronic devices and nerve tissues, so the relative shear motion of electronic devices in the brain can be minimized or eliminated. Compared with the in vivo electrophysiological recording, the number of neurons in each

of the 3D electrodes increased statistically, and the average peak amplitude, signal-to-noise ratio, and long-term stable single neuron activity study were significantly enhanced compared with the standard two-dimensional electrodes in the above aspects [14]. Comprehensive 3D inquiry, stimulation, and understanding of complex circuits in the brain and other electrical tissues have opened new opportunities for a long time.

Distributed material elements, including acoustic, electromagnetic induction, or optical methods of demonstration, are promising for treating nervous system diseases. UCNPs, the main representative of optogenetics. Near-infrared illumination has higher tissue penetration and lower light attenuation than visible light. As a powerful neuromodulation tool, optogenetics of UCNPs converts NIR light into visible light. Therefore, the possibility of producing visible light to the brain is provided by optogenetics related to UCNPs, which expands the capabilities of established optogenetics toolkits and opens up new avenues for the future generation of sophisticated neuromodulation. Neuronal diseases bring about a new phytopharmacology: UCNP offers prolonged biocompatibility, reduced invasiveness, plus better light penetration. Improving the likelihood of success and the effectiveness of neuroscience and other fields is the enhancement of optogenetics.

Wireless magnetothermal stimulation has been widely and repeatedly used to control cell signal transduction in non-excitable and electrically active cells in vitro and in vivo. To shorten the time even more swiftly between the beginning of the field and the stimulated nerve discharge, it is through developing MNPs with high specific loss power and introducing thermosensitive ion channels with low heat. The finer control of stimulation intensity can also be realized, and the application of this method in system neuroscience problems has also been promoted. The potential medium for magnetothermal inhibition is the threshold, mechanically sensitive potassium and chlorine channels. Although it has been proved that it can be used for the chronic stimulation of the target neural circuit, this magnetothermal mode can be used to trigger the heat-sensitive ion channels expressed endogenously and the wireless control of the deep tissue areas that pose a major challenge to bioelectronic has also been realized.

4. Conclusions

As four advanced materials and designs for examining brain interfaces, filamentary probes, conformal sheets, open-mesh networks, and distributed material elements advance rapidly, and their merit varies based on their distinctive qualities.

Filamentary probes are small and designed for particular brain tissue. The conformal sheet architecture comprises a flexible thin layer of membrane that connects to peripheral nerves for a greater area of contact with neuro surfaces. Stentrodes and three-dimensional electrodes are two common examples of open-mesh networks, which frequently function as mesh electronics and collect and stimulate brain activity via an intracranial electrode array. Open-meshes networks have advantages over conventional probes when recording and activating neurons in terms of consistency and long-term stability. Distributed material elements that include two dominant technologies: optogenetics and magnetic heating, employ various fields that can be absorbed and scattered by tissue. Such advanced bio-medical applications can benefit from profound neuromodulation techniques. In a word, they are all useful tools that open up an expanding number of new options and possibilities for treatments and the sophisticated study of the coming generation on neural interfaces. Their benefits, each of which holds great promise for future research, demonstrate they will thrive in the foreseeable future.

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