The Functional and Structural Evolution of Neural Implants from Biomaterials to Biointerfaces

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Abstract. Neural interfaces (NI) are now becoming a transformative platform to record and modulate neuronal activity which can be used for brain–computer interfaces, neurological diagnosis, and rehabilitation. But they are still constrained by complicated interactions between artificial materials and neural tissues in their long-term performance. Foreign body responses and chronic changes at the electrode–tissue interface caused by mechanical mismatch between the artificial materials and the neural tissue compromise the stability of electrode–tissue interactions. In the meantime, the materials deteriorate, and the interfaces between them become unstable, which leads to a higher impedance and the progressive deterioration of the neural signal. Recent breakthroughs in biomaterials and device engineering have moved the field away from standard rigid electrodes and towards integrated strategies to facilitate long-term neural integration. This review presents a summary of the development of neural implants from biomaterials to biointerfaces, covering functional and structural aspects. The first discussion concerns the development of biocompatible materials, which are moving from mechanically rigid substrates to flexible polymers, mimicking tissue hydrogels and materials with improved electrical and biological properties. In turn, interface engineering strategies such as surface modification, bioactive coatings, structural optimization, and encapsulation approaches that control tissue interactions and enhance the stability of the device are discussed. All the developments mentioned here point towards the use of complementary materials and system-level engineering for future neural interfaces to strike a balance between various types of compatibility and electrochemical performance.

Keywords: Neural interfaces, Biomaterials, Biointerfaces, Biocompatibility, Interface engineering.

1. Introduction

Driven by the deep integration of modern neuroscience and information engineering, neural interfaces have been developed to achieve active recording and modulation of neuronal activity. Brain-computer interface (BCI) systems have been further established and developed as transformative platforms for applications ranging from neurological diagnosis to functional neurological rehabilitation, as well as direct brain and external device communication [1]. Given the complex and dynamic nature of the neural system, these bioelectronic systems rely on the continuous transduction of ionic neural signals into high-resolution electronic data. However, the long-term efficacy and safety of these platforms are fundamentally constrained by the compatibility of the biotic-abiotic interface. Despite substantial progress in signal processing and algorithmic optimization, microenvironmental disturbances such as inflammation can still cause progressive signal degradation and eventual system failure [2].

One of the main problems in neural interfacing is the inherent mismatch between artificial materials and the neural tissue. A conventional electrode is typically made of a hard material and has mechanical properties several orders of magnitude different from that of soft and viscoelastic brain tissue, and is not as capable of adapting to biological tissue as necessary for stable integration. These conditions trigger a foreign body response (FBR) which involves acute tissue damage, persistent neuroinflammation and chronic tissue remodeling [3]. This encapsulation changes the extracellular matrix, hinders regeneration of neurons and creates a chronically inflamed interface between the implant and the neural tissue that is structurally and functionally different from the native neural tissue. These changes at the interface affect the ability of the nervous system to pick up signals. At the same time, the deposition of intracellular and extracellular deposits alters electrochemical

properties which results in increased resistance and decreased charge transfer efficiency. Degradation of signal is indicated by a decrease in signal-to-noise ratio, an increase in noise and a gradual loss of stable single unit recordings. Thus, biocompatibility is not just a passive measure of tissue tolerance, but it also controls the fidelity of the signal at the neuronal interface.

There has been evolution in material engineering with increasing compatibility in response to limitation of conventional neural interfaces. Flexible and ultraflexible materials have been recently studied to minimize mechanical mismatch with neural tissue and inflammation due to micromotion. One such study, for instance, showed that a hydrogel used to optimize mechanical compatibility can decrease the formation of glial scar and enhance the biological microenvironment of neural implants [4]. Conductive polymers such as poly (3,4-ethylenedioxythiophene) (PEDOT) have also been studied in parallel that can retain mechanical flexibility and low immunogenicity and at the same time reduce the interface impedance of the MEA [5]. Design strategies for neural interfaces, on the other hand, have been extensively studied recently to reduce the unwanted interfacial responses from a systems engineering point of view beyond material optimization. Interfacial engineering with biochemical modulation has been used to modulate the immune microenvironment and enhance signal quality in the nervous system.

Despite substantial advances in neural signal processing and miniaturization of devices, the long-term function of implantable neural interfaces is limited by the complex interaction between artificial devices and biological tissue. Neural interfaces should also be viewed as dynamic material–tissue systems, as mechanical mismatch, interfacial instability, and material degradation are all primary factors impacting signal quality and device reliability from an engineering perspective.

Recent studies have therefore focused on integrated material and interface engineering strategies rather than on optimizing individual electrode materials. This review presents an overview of recent developments in biocompatible materials and interface engineering for implantable neural interfaces. The development of neural interface materials is first reviewed in terms of mechanical, electrical, and biological properties. Then, engineering strategies developed to obtain long-term neural integration, such as surface modification, encapsulation and application-specific device design are discussed.

2. Evolution of Biocompatible Materials for Neural Interfaces

The properties of interface materials and their interactions with neural tissue are the critical determinants of the performance of implantable neural interfaces. Unlike traditional materials that primarily provide passive structural support, next-generation biomaterials must meet a complex set of mechanical, chemical, and biological requirements to ensure both the safety and signal fidelity of brain-computer interfaces [6].

Recent developments in biomaterials reflect the convergence of multiple design strategies. In terms of tissue compatibility, the field has transitioned from rigid substrates to flexible polymers and, more recently, tissue-mimetic matrices. Structurally, simple elemental materials are being progressively replaced by functionalized organic and composite materials with greater tunability.

2.1. From Mechanical Compatibility to Bioactive Materials

A major criterion for implanted materials is that they should be compatible with the tissue, and neural interfaces should perform consistently and without large biological responses. But once this softness was increased to some point, the optimization of tissue compatibility became more complex than it was in the past, as it became necessary to recapitulate the features of the entire extracellular matrix. Hydrogels and bio-based materials represent the latest developments in materials at this stage.

Flexible polymers can simultaneously provide mechanical compliance and strong dielectric properties, which makes them ideal structural materials and encapsulants for advanced neural interfaces. This mechanical compliance has been shown to have profound effects on the attenuation of chronic foreign body responses with diminished immune cell activation and improved maintenance of blood-brain barrier integrity in murine models. Moreover, when considering the values of softer

implants, it is possible that the mechanical compliance of polyimide has been optimized for neural probes [7]. Different biocompatible elastomers with Young's modulus ranging in the MPa can be used to develop ultra-flexible thin-film structures for brain implants [8]. Experimental data shows that PDMS is able to make softer, long-term multimodal neural interfaces that greatly reduce tissue damage and foreign body response typically seen with conventional polyimide electrodes in rats.

Conductive polymers also provide mechanical flexibility of the conductive component of interfaces. With the advantages of easy synthesis and modification, Polypyrrole (PPy) has been widely used in coating for neural interface. A study involving both in vitro neuronal culture and implantation of freestanding PPy neural implants into the rat cortex showed that PPy implants with different dopants have the ability to support the growth of neuronal networks and possess a biocompatibility that is better than that of medical grade Teflon. Their additional benefit of reduced post-implantation gliosis further bolsters their potential use as not only coating on electrodes, but also as stand-alone neural prosthetic devices [9]. Recently, by using an in vitro electrochemical assay and in vivo rat implantation experiments, Castagnola et al. showed that modifying electrodes with PEDOT: PSS can substantially reduce the electrode impedance without compromising biocompatibility and lead to an overall high signal-to-noise ratio of neural recordings [10].

Hydrogels and biobased materials, which usually have some bioactivity and mimic or recapitulate important elements of the native extracellular matrix (ECM), can diminish the mismatch between the neural interface and the ECM and, in turn, enhance the biocompatibility of the interface. Hydrogels are biopolymer networks that are able to absorb and retain a large amount of water without dissolution and are 3D networks in which the biopolymers are crosslinked to form a network. Spencer et al. have shown that polyethylene glycol dimethacrylate (PEG-DMA) hydrogels have a low elastic modulus and have improved mechanical compatibility with brain tissue. Accordingly, when applied as a coating, these hydrogels were found to greatly reduce the foreign body response and tissue damage caused by conventional, hard borosilicate neural implants in rats [11]. Furthermore, the porous and hydrated nature of hydrogels allows transport of ions and diffusion of molecules and this property has been exploited to incorporate conductive elements into the hydrogels. Chong et al. has verified that PEDOT: PSS doped hydrogels possess a composite material with the combined with the improved mechanical properties, excellent electrical performance and high electrochemical stability, which can be tunable within physiological environment [12]. In addition, hydrogels have been demonstrated to be programmable for drug transport in neural interfaces, which can help in the neural repair of stroke mouse models. This evidence clearly demonstrates that hydrogels are a bioactive interface, not just simply inert layers of encapsulation.

2.2. Conductive and Multifunctional Materials for Neural Signal Transmission

Conventional electrodes are based on simple structures of elemental metals and metal oxides, which limit their functional performance, while more advanced functionalities need more complex structural supports. The performance achievable with bioelectronic systems has become increasingly complex and, as a result, organic polymers have appeared and gradually developed more complex and functionalisable architectures. At present, studies on multifunctionalised materials with multiple binding sites for functional groups are extending the limits of the materials performance.

Carbon-based nanomaterials can be fabricated into smaller and lighter constructions, which can lessen the disruption of the tissue during the implant process, in comparison with traditional metal electrodes. Studies have shown that carbon fiber-based electrode arrays have a small footprint that reduces tissue damage, and are highly scalable to achieve high channel count and high-resolution recordings. Moreover, they have been emphasized for their long-term recording stability in vivo [13]. In addition, the electrical performance properties of graphene and carbon nanotubes (CNT) materials are also enhanced and can be tuned by the high surface area and nanoscale structure of these materials. To fabricate a flexible cortical electrode, Yang et al. used carbon nanotube arrays (CNTA) and showed that the large specific surface area and excellent conductivity of CNTs enabled the electrode to have a lower impedance and higher capacitance and charge storage than traditional gold electrodes.

The ion–electron transduction property of the CNTs will allow the electrodes to pick up both electrophysiological and chemical signals. Moreover, CNTs can be combined with a PDMS substrate to create mechanically adaptive neural interfaces that displayed minimal inflammatory responses and good biocompatibility in in vivo implantation [14].

MXenes are a new family of transition metal carbides, nitrides and carbonitrides with the general chemical formula $M_{n+1}X_nT_x$., where M, X and T are a transition metal, carbon or nitrogen, and surface functional groups, respectively. The two-dimensional nanostructure gives it its metallic conductive property and high electrochemically active surface area; and the surface functional groups give it excellent water solubility, low immunogenicity, high cell adhesion, and processability. These properties can enhance the biocompatibility and electrochemical properties of neural implants, and can facilitate drug loading and flexible material processing, making the material a promising material for future neural implants [15].

3. Interface Engineering for Long-Term Neural Integration

The design space of neural interfaces has expanded with advances in biomaterials. But no single material will be able to optimize the mechanical, electrical, and biological performance simultaneously [16]. Interface engineering, as a result, is an important aspect of how the various materials are integrated into the entire device to ensure long-term performance. Surface modification at the electrode–tissue interface will enhance electrochemical function and modulate interactions at the electrode–tissue interface. Finally, on the device level, there are functions to reduce a biomechanical mismatch in architecture and functions for the protection of electronic components and the optimization of operational lifespans by encapsulation technologies [17].

3.1. Surface Engineering and Interfacial Regulation

Bulk materials determine the mechanical and structural characteristics of the neural interfaces, and surface properties directly impact electrode-tissue interface. To optimize the interfacial interactions, therefore, surface modification by functional coatings and drug-eluting layers are employed [18].

Electrochemical or solution-based deposition can be used to deposit conducting polymers, carbon-based nanomaterials, and conductive hydrogels on the surface of an electrode. They possess micro and nanostructures with the effect of enhancing the electrochemically active surface area, the charge transfer, and they decrease the impedances. Such coatings can also be thin, conformable, and improve the mechanical compatibility, while maintaining electrical connectivity [16]. In general, such materials are able to produce nano-structured surfaces with a high electrochemically active surface area. In contrast to carbon-based nanomaterials, where the inherent nanoscale morphologies and architectures of materials play a major role, conducting polymers are likely to develop 3D microstructures during deposition. Further, the alternating single double-bonded conjugated structures of conducting polymers enable efficient electronic transport and allow reversible changes of oxidation state, that is to say to increase the charge injection capacity of the polymer. Carbon-based nanomaterials on the other hand use the conjugated carbon framework to facilitate an efficient electronic transport. In addition to the electrochemical properties, conducting polymers and carbon-based nanomaterials can be deposited in thin, flexible and conformable formats to minimize the mechanical mismatch between rigid electrode substrates and soft neural tissues. The relatively flexible polymeric structures and tunable film architectures of conducting polymers can offer mechanical compliance, and the carbon-based nanomaterials can form nanoscale networks that conform with the underlying electrode surface without compromising electrical connectivity. Moreover, conductive hydrogels can be used as coating materials on the electrode, primarily to enhance the mechanical and biocompatibility of the electrod and tissue interface. More significantly, they can be used as platforms on which other conductive components can be integrated to come up with improved performance [17].

Coatings may also be functionalized with cell-adhesion molecules, neurotrophic factors or anti-inflammatory agents in addition to being electrochemical and mechanically optimized. For molecules that promote neuronal attachment, immobilization can be used and for drug-eluting coatings, local and controlled delivery of functional compounds can be achieved. These strategies enable the interface to control local tissue interactions, instead of passively serving as an electrode surface. In summary, surface engineering is a process that involves electrochemical improvement, mechanical adaptation of surface properties, and local functionalization to promote stable contact between the electrode and tissue [18, 19].

3.2. Structural Engineering and Application-Specific Design

The interface between neural implants and the surrounding tissue is not just on the surface, but also determined by the general design of the device. Tailoring the topology of devices that are implanted in the body can reduce mechanical constraints placed on the neural tissue using structural engineering. The physiological environment around an implant is also aqueous and ion-rich, which can cause chemical degradation of the implant, and thus encapsulation is important to protect the internal components and ensure long-term functional stability.

Structurally tuning the dimensions, geometry and structural continuity of the implanted device is three different design strategies to compensate for mechanical mismatch. In recent years, ultraflexible microwire neural electrodes fabricated using shuttle-assisted methods have been demonstrated to promote chronic tissue integration and serpentine geometry has been a subject of interest for its geometric compliance to mechanical deformations. However, open-network architectures can also decrease the volume of a continuous device and enable tissue-level integration for neural recording and stimulation, and could be a key structural paradigm for future neural interfaces [20]. In the longer-term, neural dust would enable device miniaturization to work towards a wireless and distributed microscale implant, which would be a more futuristic vision of next generation BCIs. These strategies, in combination, enable the evolution of neural interfaces from mechanically constraining bulk implants to smaller, spatially distributed and compliant systems [16].

While surface engineering aims to preserve the device surface, for encapsulation the goal is to ensure the protection of the whole device and make it correspond to the desired implantation time. Chemically stable materials like diamond-like carbon and silicon carbide can be used as protective barrier layers to prevent corrosion and degradation in physiological conditions, for chronic neural interfaces. In general, however, they are less mechanically compliant than neural tissue and are generally very thin, being used as a protective layer or internal layer in conjunction with a flexible substrate and biocompatible surface coating [21]. Biodegradable encapsulation strategies, on the other hand, are more appropriate to transient devices that can be controlled to degrade after the desired use time has elapsed. For this reason, materials that are biodegradable, like the silk fibroin or poly (lactic-co-glycolic acid) (PLGA) may be used in the temporary substrates, coatings, or structures to minimize extended exposure to foreign materials and possibly prevent further removal surgery [22]. All the point to the fact that encapsulation design should provide controllable device lifespans optimized for the practical use of the device and provide a balance of multiple conflicting requirements.

Modular designs that employ a combination of different materials to perform complementary roles are becoming more and more common in modern neural interfaces. Flexible substrates are used to achieve mechanical compliance and conductive components are used to achieve neural recording or stimulation, bioactive coatings are used to control tissue-device interactions, and stable or biodegradable layers are used to control device lifetime. These components can be combined to achieve application-specific neural interfaces that are both mechanically compatible and electrically functional, biologically interactive, and operationally stable.

4. Conclusion

As neural interfaces are developed, there has been a gradual evolution from optimizing individual biomaterials to the coordinated integration of biomaterials and system level design. Biomaterials have evolved to be more functional, from the mechanical properties of neural tissue to the ability to mimic some of the important properties of the biological microenvironment while still supporting electrochemical functions. Material systems have also progressed from rather simple compositions to more complex and functionalizable architectures that enable the integration of diverse properties needed for advanced neural interfaces. The inherent compromises between these properties, however, render the ability to meet all of the various, and sometimes contradictory, requirements of chronic neural implantation in any single material.

In addition to material selection, long-term neural integration also requires coordinated interface and device engineering. Surface modification enhances contact between the electrode and tissue and allows for local biological regulation while structural engineering diminishes mechanical constraints with miniaturized, compliant and open network designs. Encapsulation also provides added protection for the internal parts and enables the device's lifetime to be matched to chronic or transient implantation. All these strategies are part of a more general shift from the optimization of a single material to the engineering of entire, application-specific neural interface systems.

Future studies should thus be directed towards the synergistic combination of complementary materials, surface treatment, structural design, and encapsulation strategies. Instead of simply seeking out one material that will work best, next-generation neural interfaces will demand coordinated system-level design that takes into account neural compatibility, signal performance, chemical stability, and operating lifetime. This integration will be critical for developing successful neural interfaces that can function reliably and over extended periods of time from advanced biomaterials.

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